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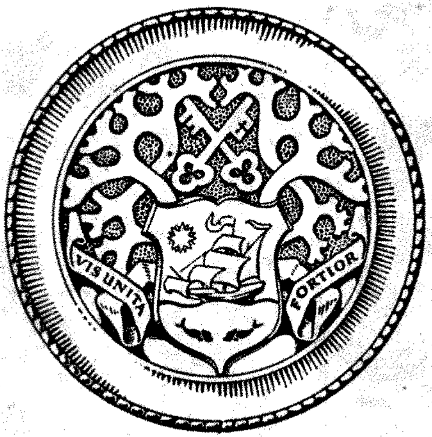

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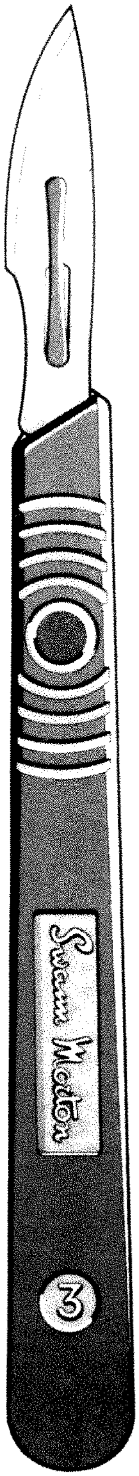

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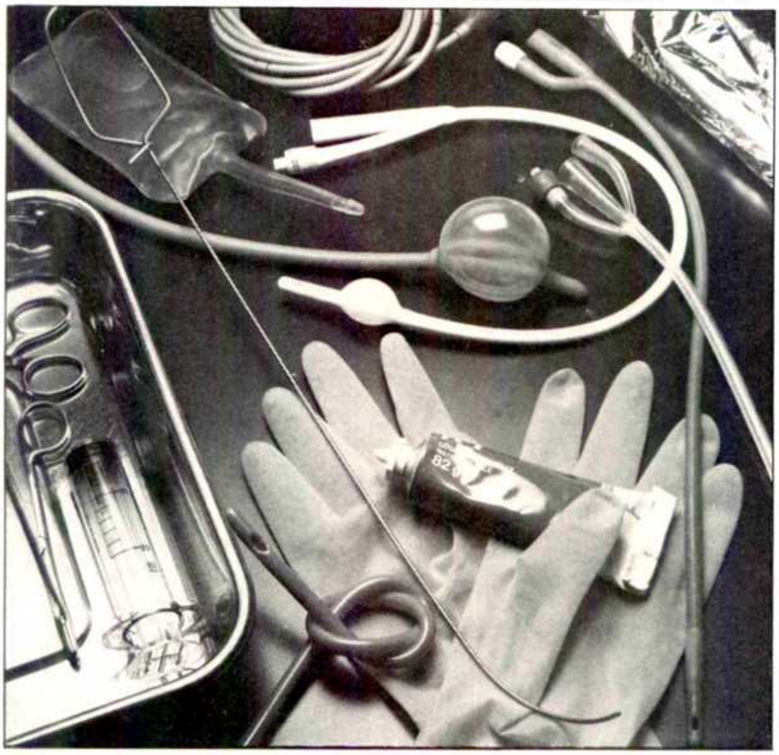

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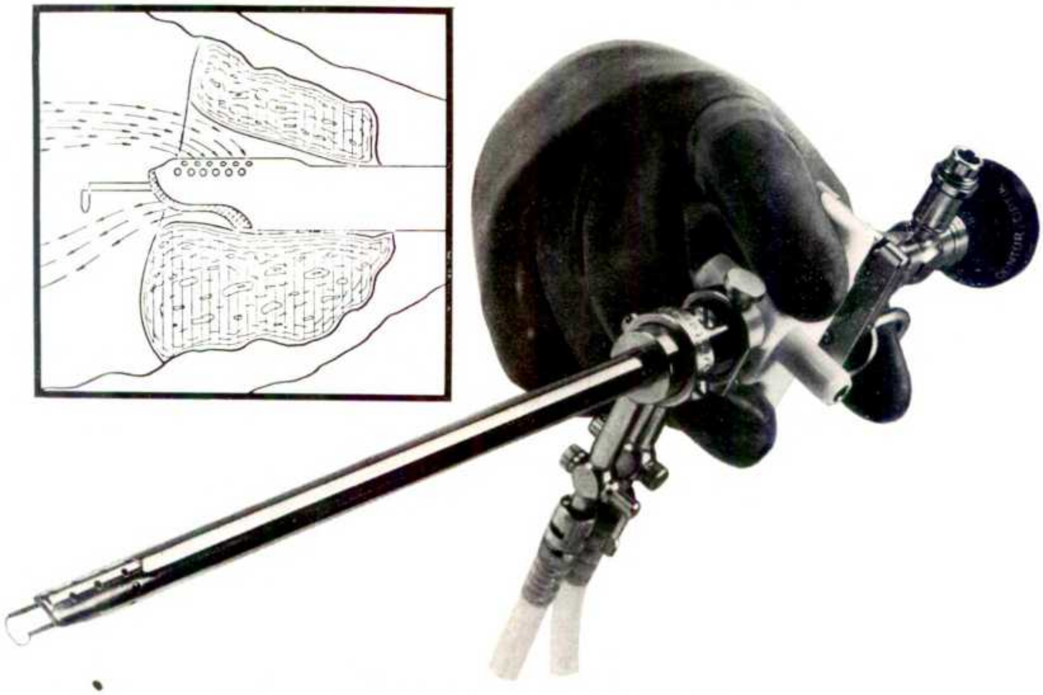

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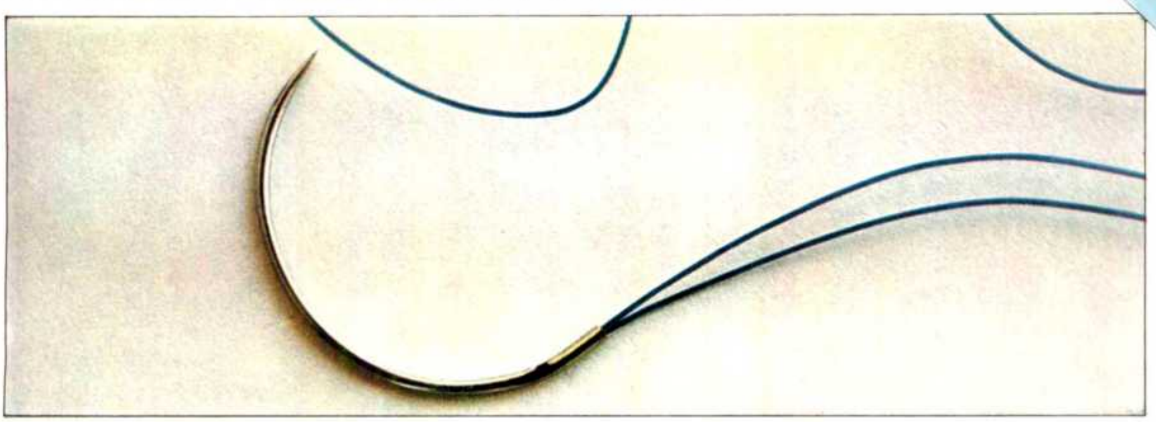

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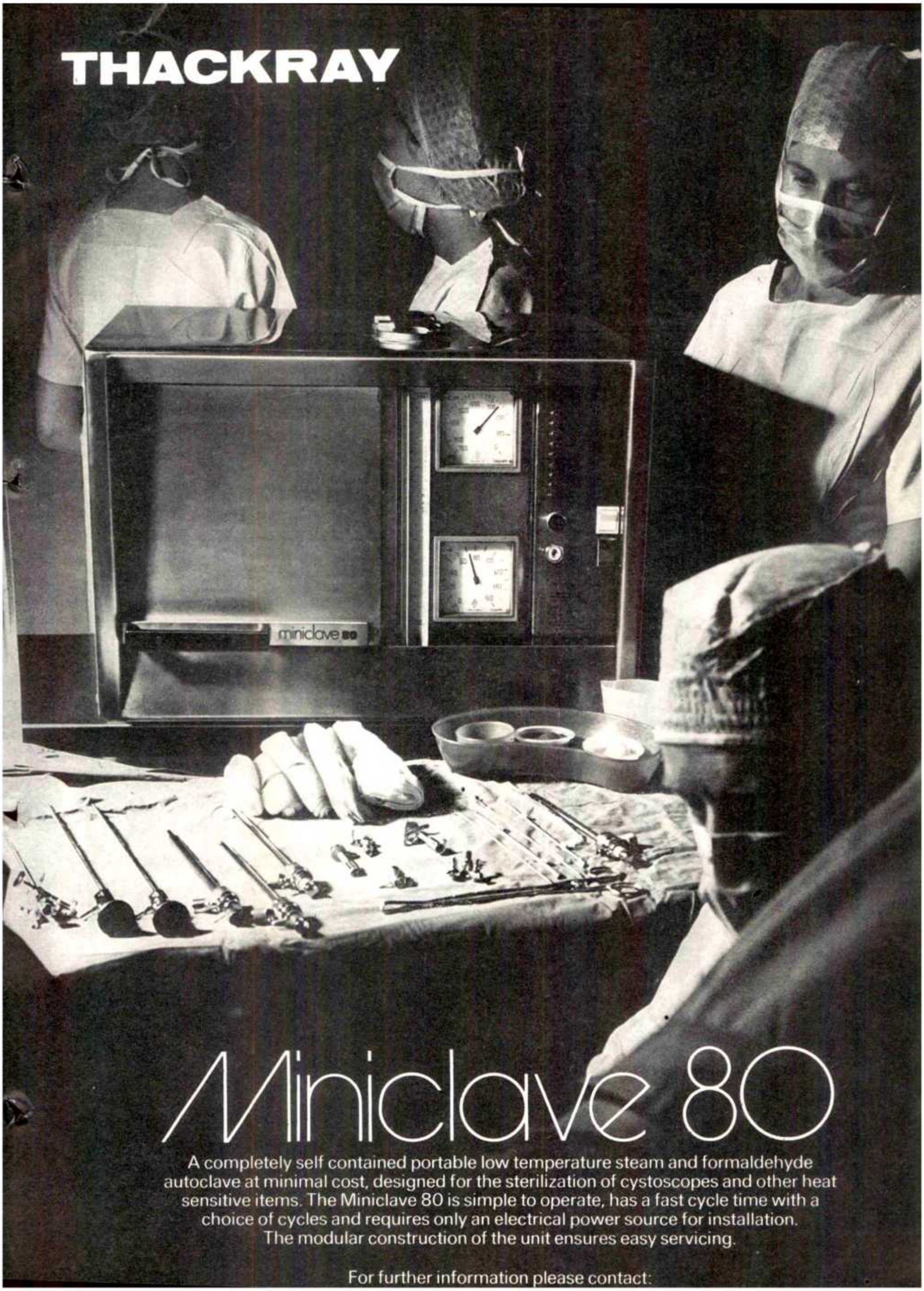

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Seasonal Variations in Urinary Excretion of Calcium and Oxalate in Normal Subjects in Patients with Idiopathic Hypercalciuria

P. C. HALLSON, G. P. KASIDAS and G. ALAN ROSE
St Peter's Hospitals and Institute of Urology, London

(Received 9 July 1976; accepted for publication 29 September 1976)

It was reported by Robertson *et al.* (1974, 1975) that urinary calcium values of normal subjects and of patients with idiopathic stone formation were higher in the summer than in the winter. The magnitude of the changes was considerable; thus, for males with idiopathic stones the mean urinary calcium was 5·7 mmol/24 hours in December and 9·3 mmol/24 hours in July. It seems surprising that changes of such a size had not been noticed previously and it was therefore decided to see if those results observed in Leeds could be confirmed in London. 2 separate studies of urinary calcium have been undertaken. The first study was retrospective and was based upon urinary calcium values observed over a 9-year period in a single metabolic stone clinic where the same patients with idiopathic hypercalciuria had attended and brought 24-hour urine collections repeatedly for many years. All of the patients were observed at first untreated, but many were subsequently treated either with thiazide diuretics or cellulose phosphate. The data was therefore not only viewed as a whole but also subdivided according to the treatment. Many of these patients have been the subject of a previous report (Rose and Harrison, 1974). The second study was prospective and based upon a group of normal individuals each of whom collected a single 24-hour specimen of urine every month for 13 consecutive months.

A new enzymatic method for the measurement of urinary oxalate was reported from these laboratories recently (Hallson and Rose, 1974). Since this method is specific and accurate within the normal range, it was thought of interest to extend the study of seasonal variations in urinary calcium to include oxalate. Accordingly, urinary oxalate was measured on every urine sample in the prospective study, and a 2-year study was also made of urinary oxalate in the patients with idiopathic hypercalciuria.

Methods

All urine collections were made as out-patients. The patients received written instructions on how to make the collections. Containers issued to patients contained 5 ml Conc. HCl prior to issue, and were normally returned to the laboratory on the day that the collection was completed. Creatinine was invariably measured and by Auto-Analyser. Calcium was measured by emission flame photometry (MacIntyre, 1957), except that during the last few months of the study a change was made to atomic absorption flame photometry. It was demonstrated that this change in method did not alter values obtained for urinary calcium. Oxalate was determined by the enzymatic method of Hallson and Rose (1974).

Diagnosis of idiopathic hypercalciuria was as previously described by Rose and Harrison (1974). The thiazide diuretic used was almost invariably bendrofluazide, the dose was usually 5 mg per day, sometimes rising to 10 mg

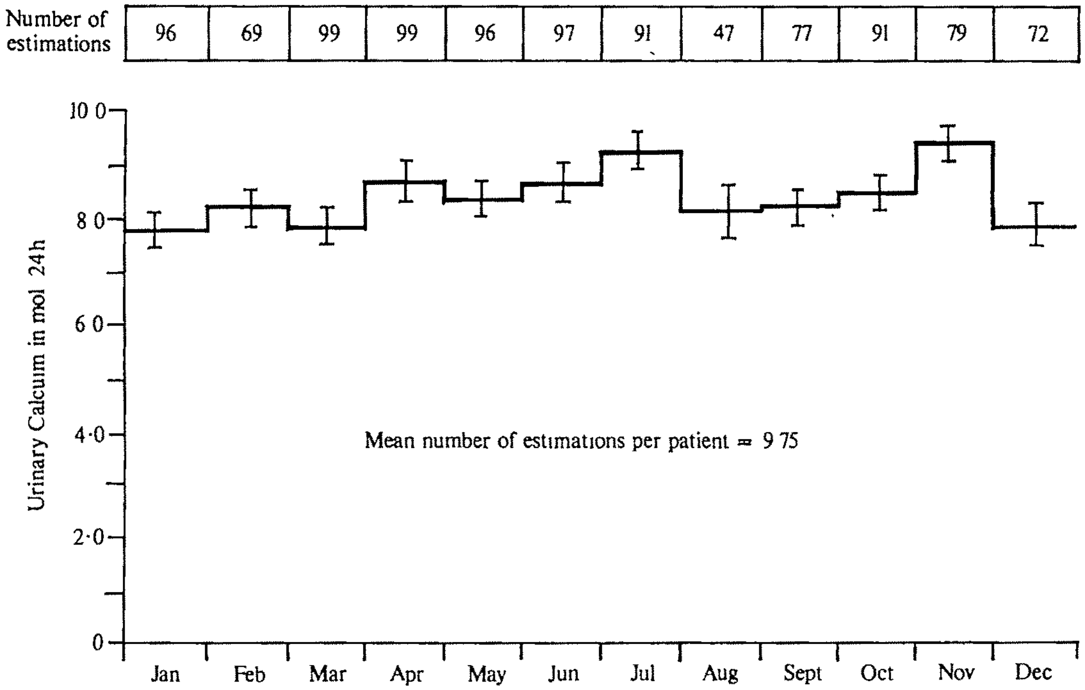


Fig. 1. Monthly variation in values for 24-hour urinary calcium of all male patients (treated or untreated) with idiopathic hypercalciuria. Thin vertical lines indicate S.E.M. The mean number of estimations per patient was 9·75.

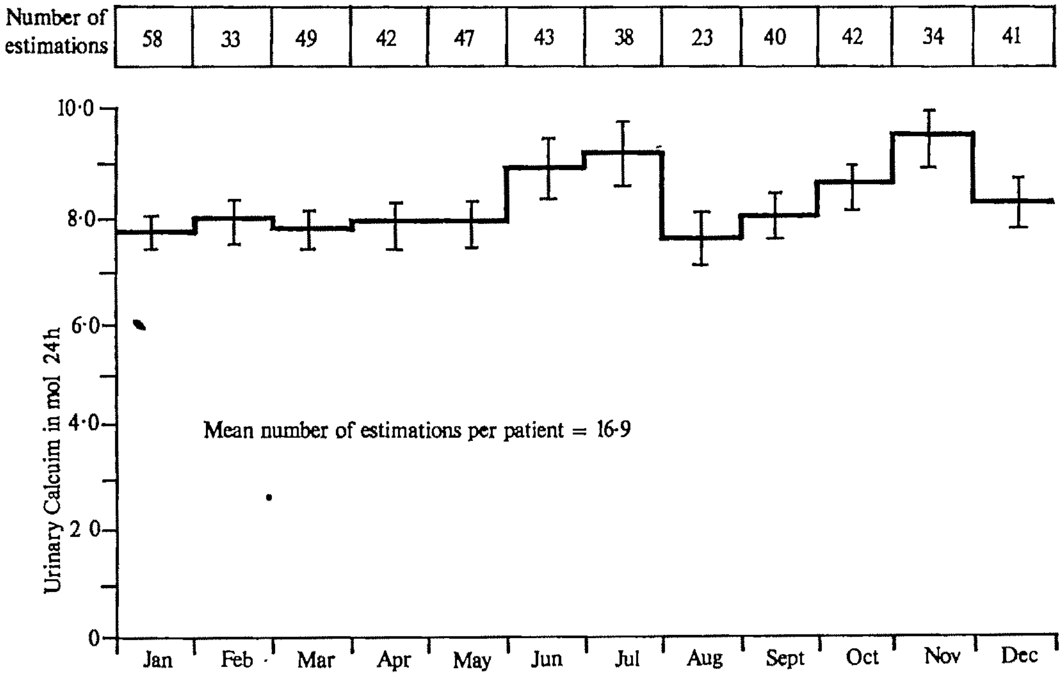


Fig. 2. Monthly variation in values for 24-hour urinary calcium of male patient with idiopathic hypercalciuria while on treatment with thiazides. Thin vertical lines indicate S.E.M. The mean number of estimations per patient was 16·9.

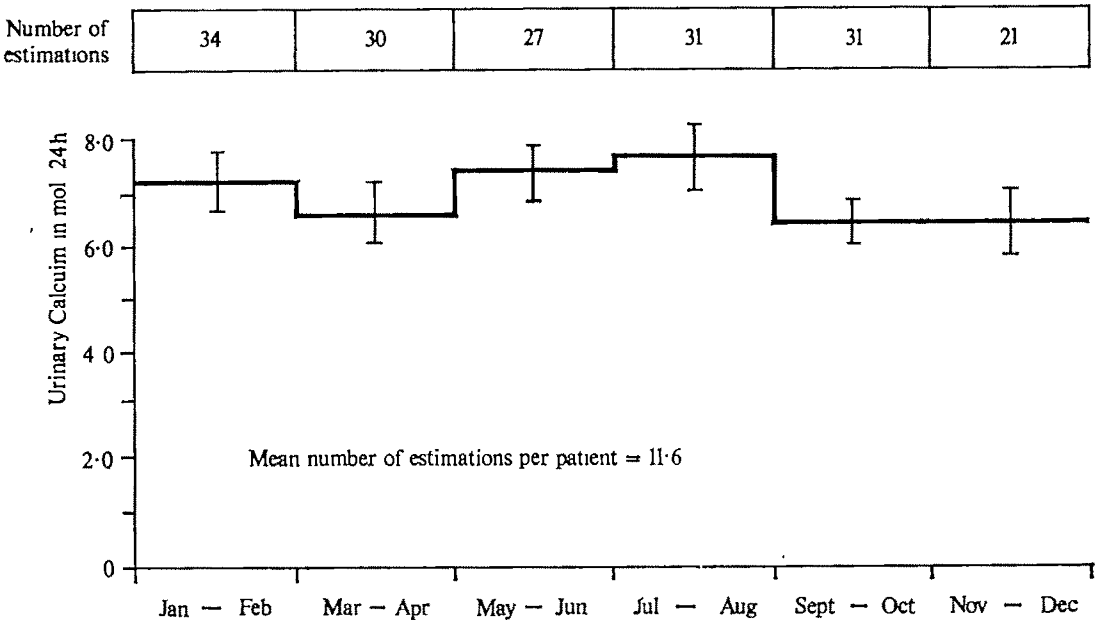


Fig. 3. Bimonthly variation in values of 24-hour urinary calcium of male patients with idiopathic hypercalciuria while on treatment with cellulose phosphate. Thin vertical lines indicate S.E.M. Mean number of estimations per patient was 11·6.

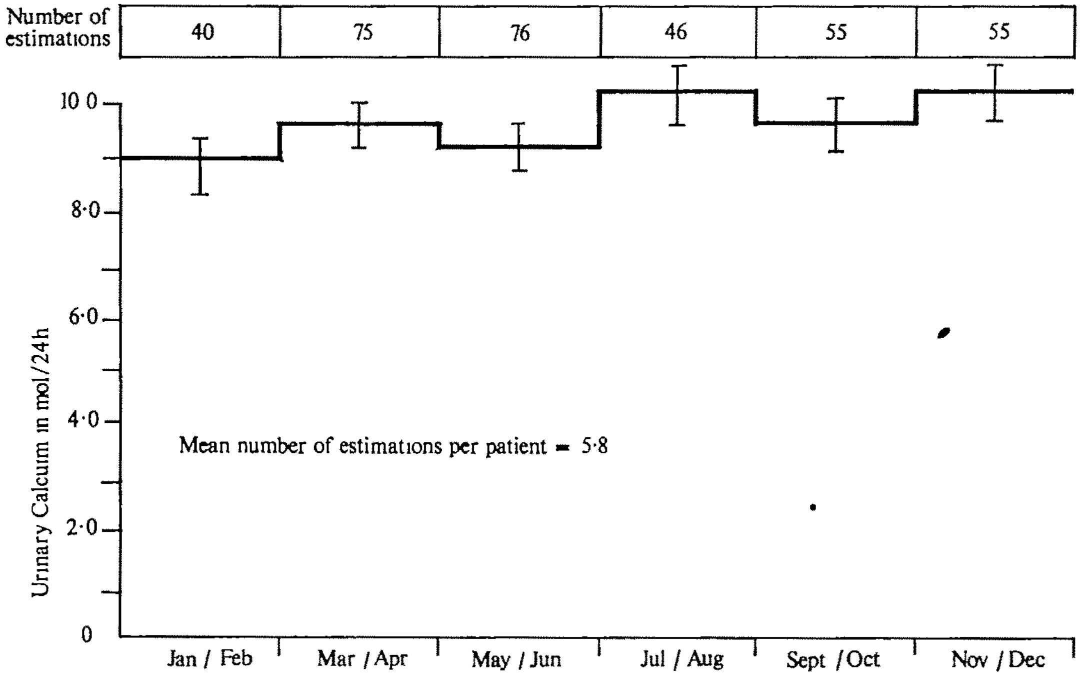


Fig. 4. Bimonthly variations in values for 24-hour urinary calcium of male patients with idiopathic hypercalciuria who were either untreated or treated only with mild calcium restriction. Thin vertical lines indicate S.E.M. Mean number of estimations per patient was 5·8.

per day. Cellulose phosphate was administered in the sodium form in a dose of 10 to 30 g per day and taken with meals.

Information on hours of sunshine and mean daily temperature for each month were obtained from the London Weather Centre.

Results

The monthly variation in urinary calcium values for all patients with idiopathic hypercalciuria, whether treated or not, is shown in Figure 1. In Figure 2 the same data is shown but restricted to

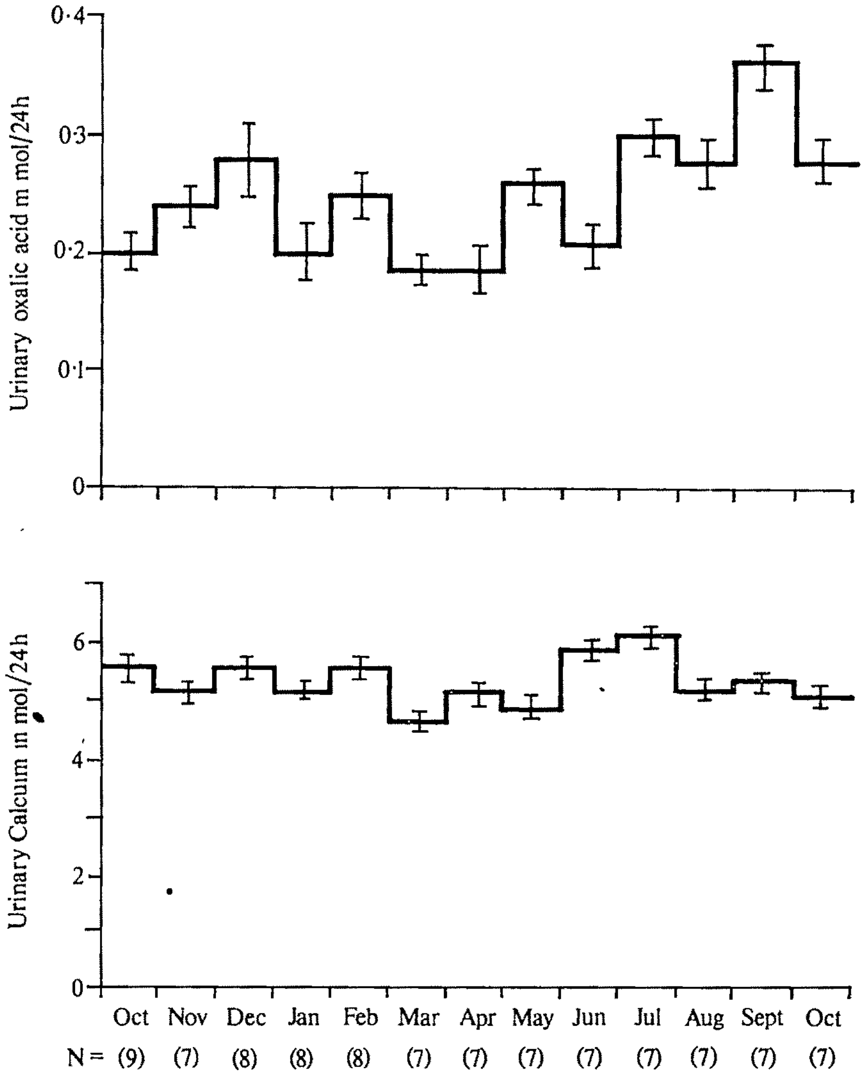


Fig. 5. Prospective study of 24-hour urinary calcium and oxalate values measured each month in a small group of normal volunteers. Thin vertical lines indicate S.E M.

those patients receiving thiazide diuretics at the time. Figure 2 shows the data for patients undergoing treatment with cellulose phosphate, and Figure 4 shows the data for patients without treatment at the time. In Figure 3 and 4 it has been necessary to plot as 2-month periods, rather than as 1-month periods, because of the smaller number of samples available. It is clear, however, that no significant seasonal variations in urinary calcium can be observed in any of these figures.

Results from the prospective study are shown in Figure 5. It can be seen that there is no significant change in urinary calcium values obtained from the normal volunteers over the 13th month period. Changes in urinary oxalate are very small, with a slight rise in the 4 summer months which does not, however, achieve statistical significance. Figure 6 shows that the urinary oxalate values of the patients with idiopathic hypercalciuria did show seasonal changes with values rising appreciably in the summer months. Results from normal subjects and patients are contrasted in Figure 8, which shows that there is a statistical difference between results from summer and winter months only in the case of the patients with idiopathic hypercalciuria. Figure 7 shows that

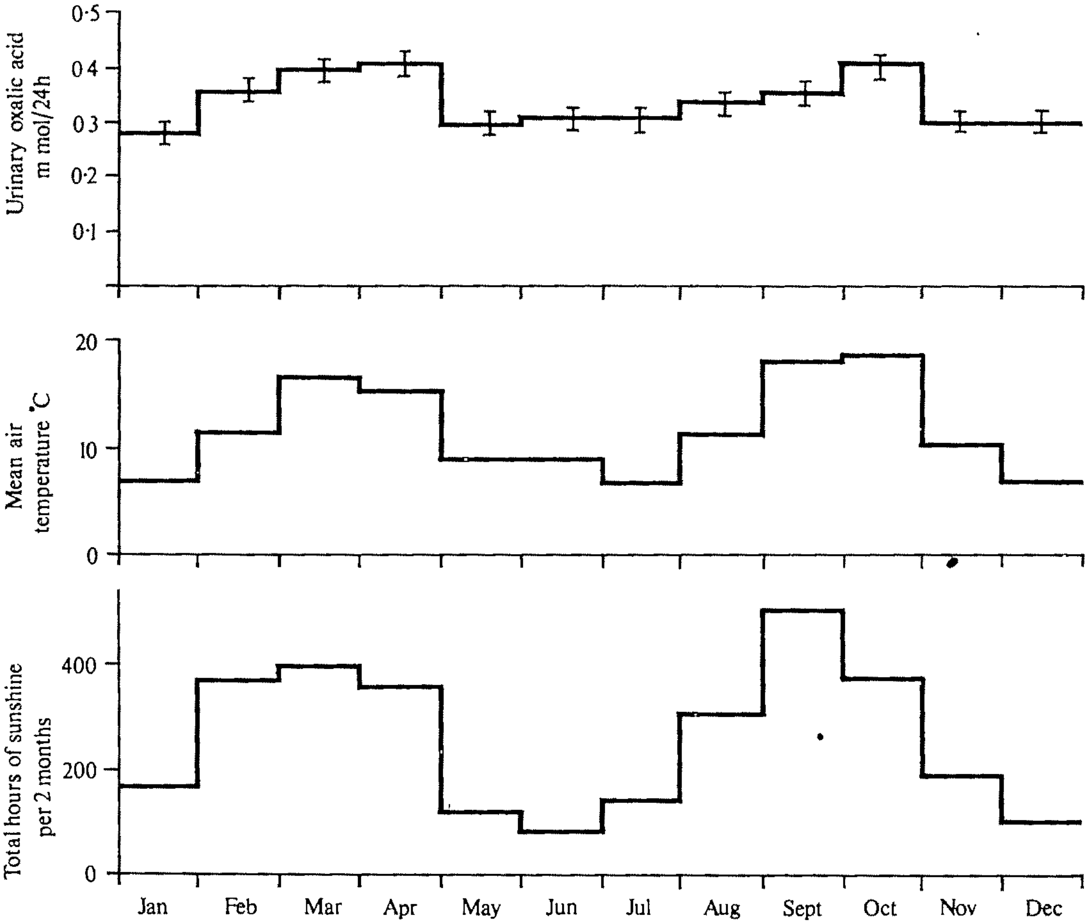


Fig. 6. Bimonthly values in urinary oxalate of male patients with idiopathic hypercalciuria, mean air temperature, and hours of sunshine for 24 successive months. Thin vertical lines indicate S.E.M.

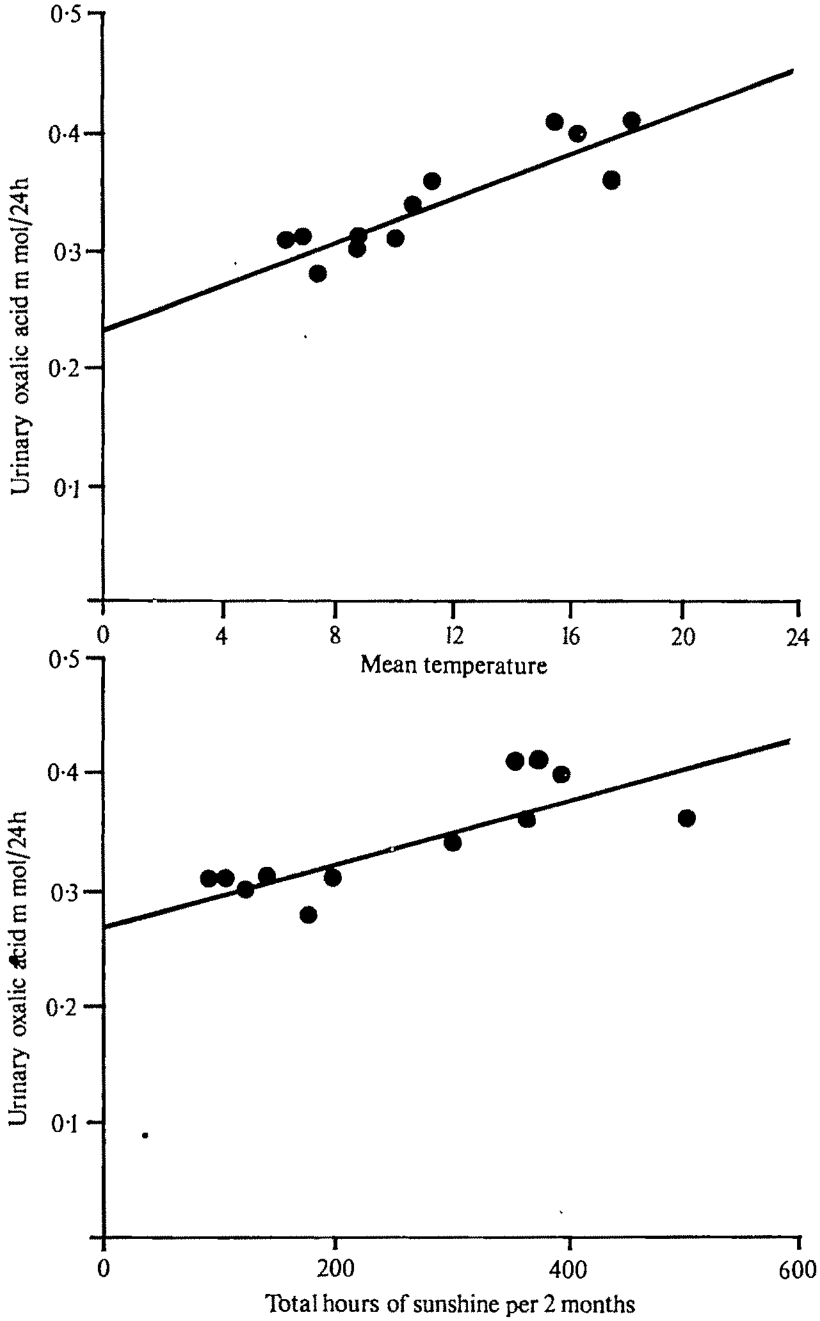
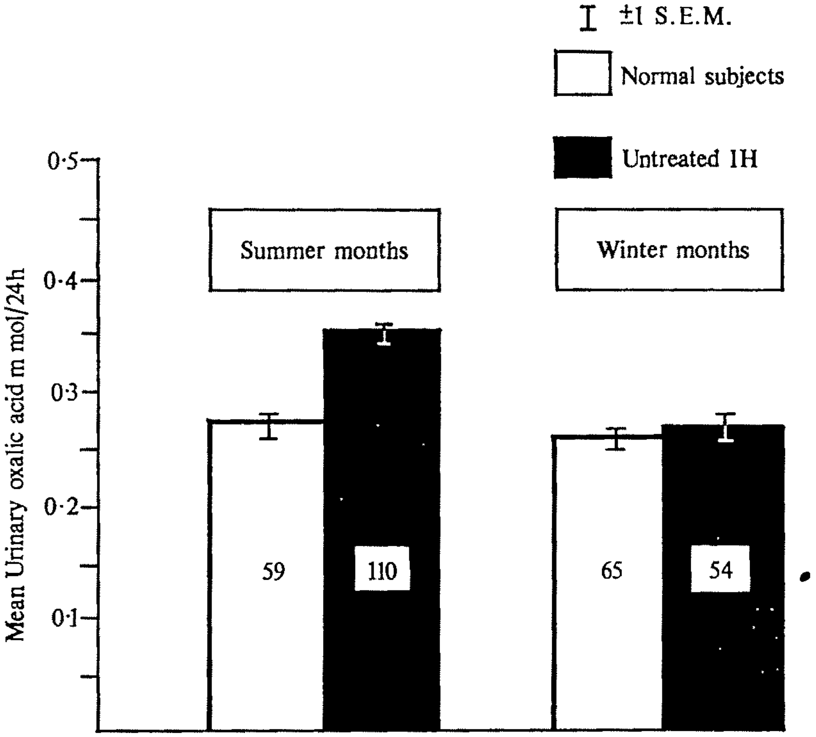


Fig. 7. Same data as in Figure 6 plotted to show correlations and regression lines. For oxalic and mean temperature R = 0·89; for oxalic and hours of sunshine R = 0·80.

the correlation coefficient between bi-monthly urinary oxalate values and mean monthly temperature is 0·89, slightly better than the correlation coefficient of 0·80 between bi-monthly urinary oxalate and hours of sunshine, although the difference between these two correlation coefficients does not achieve statistical significance.

Discussion

It has been conclusively shown that in a clinic serving the London area and the surrounding region there are no seasonal changes in urinary calcium. Neither were there any such changes in a group of normal volunteers. Admittedly, the numbers in the latter group were small, but nevertheless the result is so clear-cut that it seems unlikely that an increase in the numbers could have altered the result. The lack of change of urinary calcium with season comes as no surprise because it is felt that any change of the magnitude described by the Leeds group would have been noticed a long time ago had it occurred in London. The question now arises is why such different results should be reported in London and Leeds. First, the 2 studies need careful examination to see if they are comparable. It must be noted that the London retrospective study is a longitudinal study in which each patient was observed on many occasions, whereas the Leeds study was of



	t	p
Normals: Untreated IH in summer months	3·92	< 0·005
Normals: Untreated IH in winter months	0·24	< 0·49

Fig. 8. 24-hour urinary oxalate values in 6 summer and 6 winter months for normal subjects and untreated males with idiopathic hypercalciuria. Thin vertical lines indicate S.E.M. Note that values for the normal subjects are the same in summer and winter and the same as for the patients during the winter. Only the patients showed a rise in the summer months.

the cross-sectional type in which each patient contributed once only. The cross-sectional study can be influenced by extraneous factors unwittingly introduced. Thus if any factor was at work which caused hypercalciuric patients to present in the summer rather than the winter, then it would appear that hypercalciuria was more common in the summer whereas this might not be so. That such factors were at work seems rather likely. Thus, it was found by Black (1945) that oxaluria was most common in the British Army in India during the hot months. Also, Pierce and Bloom (1945) reported that the incidence of renal stones amongst US troops in the desert was greatest in the hot months. Furthermore, Robertson *et al.* (1975) themselves clearly show that the incidence of spontaneous passage of stones in their patients was highest in the summer months, perhaps because the urine collections were made soon after these episodes. Hence 1 possible cause of bias clearly exists and there could be others of which we are unaware. Secondly, however, the possibility must be considered that there is in fact a true difference between the populations of the Leeds and London areas respectively. If this is so, is the difference occurring in the summer, or the winter, or in both? Comparison of the data from the 2 studies shows that the summer values for urinary calcium agree in the 2 areas and that it is in the winter that the differences occur, the London patients failing to show the fall from the summer levels of urinary calcium shown by the Leeds patients. Robertson *et al.* (1974) have attributed the seasonal changes they observed, at least in part, to changes in exposure to sunlight. If this view is correct, it would follow that in London the level of exposure to sunlight does not change appreciably between summer and winter in contrast to Leeds. Although Leeds is 180 miles north of London, this proposition does not seem likely to be true, and indeed it could be argued that the absolute difference in exposure to sunlight between summer and winter is greater for London than in Leeds.

At the outset of this study we were unaware of any other observations of seasonal variations for urinary oxalate. Recently, however, Robertson *et al.* (1975) confirmed our preliminary report (Rose and Hallson, 1975) that patients with idiopathic calcium stone formation show rises in urinary oxalate during the summer months. These authors did not, however, study normal individuals. It has been shown here that in a small group of normal subjects there was no difference in urinary oxalate values between the summer and winter months. On the other hand, the patients with idiopathic hypercalciuria, in a longitudinal 2-year study, showed a rise in urinary oxalate in the summer months which was seen in each of the 2 successive years. 1 possible cause of the rise in urinary oxalate in the summer months might be that it is related in some way to vitamin D obtained from sunlight. Since, however, it has been shown above that urinary calcium is unchanged between summer and winter, this explanation is rendered unlikely. Furthermore, Figure 7 shows that the correlation between urinary oxalate and hours of sunshine is not as good as that between urinary oxalate and mean temperature. This suggests that an increase in oxalate in the diet for the summer months might be a more likely explanation, and certain known facts support this theory. Firstly, some of the oxalate-rich foods, namely rhubarb, spinach and beetroot, are seasonal and consumed more in the summer than in the winter. Secondly, Archer *et al.* (1957) found that when healthy normal volunteers received standard sodium oxalate supplements to their diet, the rise in urinary oxalate accounted for 3% of the oxalate given. Marshall, Cochran and Hodgkinson (1972) found that the rise in urinary oxalate produced by a standard oxalate load was increased to 8·1% by a low calcium diet and reduced to 3·6% by a high calcium diet. Similar results were reported by Villarino *et al.* (1972). It should be noted here that all the patients with idiopathic hypercalciuria had been prescribed a low calcium diet with restrictions of milk, cheese and related foods. Hence there is a ready explanation for the fact that the patients, but not normal subjects, showed a rise in urinary oxalate in the summer. To see this rise, not only must there be an increase in intake, but the individuals must have a low faecal calcium. Such a low faecal calcium results from a low calcium diet together with relative hyperabsorption of dietary calcium.

It is of interest that these seasonal changes in urinary oxalate have been observed only very recently. 2 possible explanations for this may be offered. Firstly, the measurement of urinary oxalate has been tedious and lacking in precision and accuracy so that few estimations have been undertaken in the past and the results are of doubtful value. On the other hand, using the enzymatic method described, it has been possible to undertake large numbers of measurements and obtain reliable results within the normal range, so revealing the facts described. Secondly, it should be noted that there are in the literature some suggestions that urinary oxalate may be raised in idiopathic hypercalciuria or idiopathic stone formation (Revúsova, Zvara and Gratzlová, 1971; Thomas *et al.*, 1973), without however clear indication of the season of the year or whether the patients were on normal or low calcium intake. It is therefore possible that seasonal variations have been seen but not recognised. It is clearly important in future work that both the season of the year and the diet should be clearly identified.

Summary

A longitudinal 9-year retrospective study of 24-hour urinary calcium values has been made in a metabolic stone clinic amongst patients with idiopathic hypercalciuria. No seasonal variations could be observed in contrast to a previous study from Leeds.

A prospective longitudinal study was made of 24-hour urinary calcium values in a small group of normal subjects. No seasonal variation could be observed.

In the prospective study no seasonal variations in urinary oxalate could be observed.

In a 2-year longitudinal study of stone patients with idiopathic hypercalciuria, urinary oxalate was found to be higher in the summer than in the winter. This was attributed to the combination of a higher intake of oxalate-rich foods in the summer, and the low calcium diet with which they were treated.

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Renal Phlebography in Hydronephrosis

FABIO FLORIS
Clinica Urologica dell'Universita, Ospedale Maggiore, Trieste

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While the renal arteriographic pattern in hydronephrosis is well known (Idbohrn, 1956; Laubenberger, 1969; Leary *et al.*, 1972), nothing has yet been reported on renal phlebography in this condition. The purpose of this paper is to report our observations on the phlebographic pattern in hydronephrosis.

Patients and methods

Our first observations in the field were made 3 years ago by checking the exact position of a catheter before taking blood samples from the renal vein for renin determination in a hypertensive patient with kidney dilatation. Because of the peculiarity of the phlebographic pattern observed, we have visualised the renal venous tree in another 24 hydronephrotic patients during the course of obtaining samples of blood for renin. Hydronephrosis in these patients was of various aetiology and degree. In 17 cases hydronephrosis was of mild degree, in 4 cases it was marked and in 4 cases there was a secondary infection and complete disruption of the kidney. The age range was from 20 to 62 years.

The visualisation of the renal vein and its branches was obtained by injecting, under pressure, 10-15 ml of contrast medium through a catheter passed transfemorally.

In 3 patients both renal arteriography and renal phlebography were performed.

Results

The most characteristic phlebographic aspect of a hydronephrotic kidney is the visualisation of a complete anastomosis among the branches of the renal vein (Figs. 1 and 2) which is not evident in normal human kidneys *in vivo*. There is often elongation of the first branches of the renal vein due to enlargement of the pelvis and the renal cavities (Fig. 2). The calibre of the venous branches may vary according to the injection pressure used.

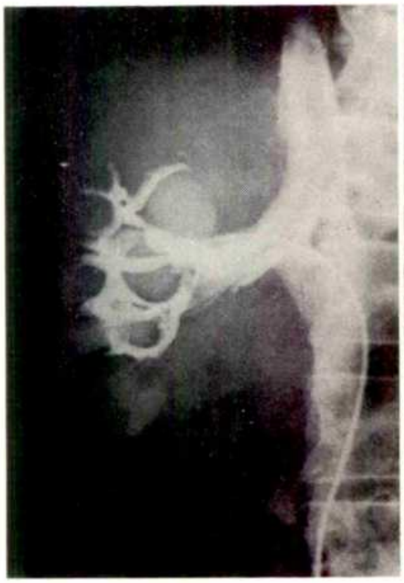
In 4 cases of hydronephrosis in an advanced stage there was a fine venous network located peripherally to the previously described anastomosed branches (Fig. 3).

In 4 cases of secondary infection in which a complete disruption of the kidney was confirmed during subsequent surgery, the branches of the renal vein were not visualised (Fig. 4).

In 3 patients with hydronephrosis of mild degree in which both arteriographic and phlebographic studies were performed the alterations of the phlebographic pattern were more marked than the arteriographic ones.

Discussion

The characteristic phlebographic pattern in hydronephrosis of a mild degree is the visualisation of free extraparenchymal anastomoses of the branches of the renal vein. These anastomotic branches, situated in the renal sinus, have been clearly described by Piasecki, Jugowski, and



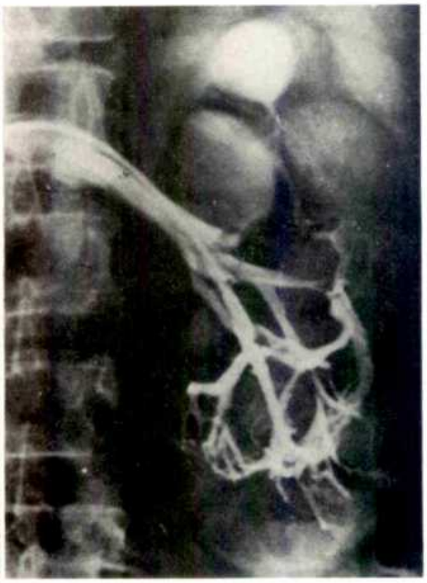
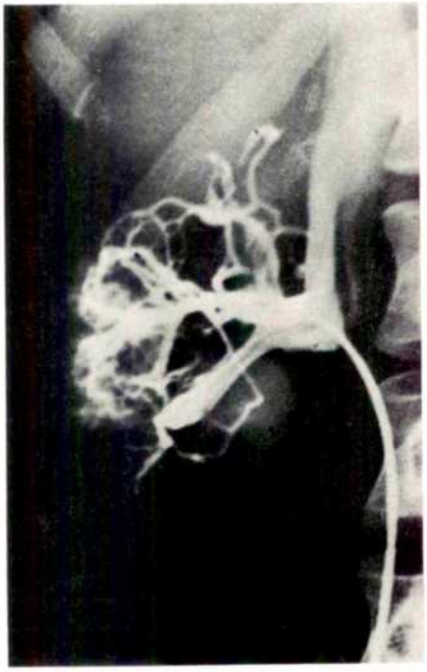


Fig. 1. Right renal phlebography of a mildly hydronephrotic kidney: free anastomoses among the branches of the renal vein.

Fig. 2. Left renal phlebography (trunk and inferior branches) of a hydronephrotic kidney in a more advanced stage. The branches of the renal vein are elongated and freely anastomosed. Some contrast medium passes into the interlobar veins.



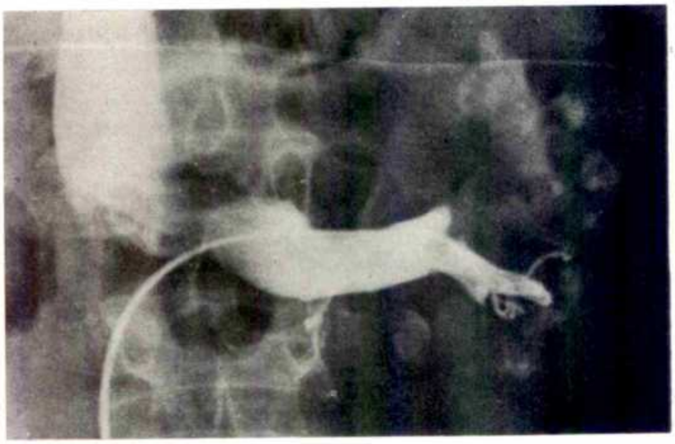


Fig. 3. Right renal phlebography of a hydronephrotic kidney that previous urographic and renogram studies have shown to function poorly. There is a fine venous network peripherally, in the parenchymal area.

Fig. 4. Left renal phlebography of a hydronephrotic calcotic kidney shown upon surgery to be completely destroyed: lack of visualisation of the branches of the renal vein.

Piotrowski (1964), who studied the renal venous system by the cast technique. They are evident through venous contrast medium injection *in vivo* only in a hydronephrotic kidney, whereas in an isolated kidney they are visualised even when hydronephrosis is not present (Gerard and Castiaux, quoted by Dalla Palma and Servello, 1956).

To explain why these anastomoses are evident *in vivo* only in hydronephrosis, even though they are present in normal kidneys, several things must be taken into consideration: first of all the visualisation of the renal venous system, achievable only by retrograde injection of contrast medium, causes a haemodynamic interference and what appears in phlebographic studies is the visualisation of this interference rather than the true situation of the renal venous system. On the other hand one must consider that in hydronephrosis there is a rise in intrapelvic pressure that reflects on the parenchymal structures and therefore in the veins (Gottschalk and Mylle, 1956). It is likely that this secondarily enhanced pressure in the intrapelvic veins prevents the contrast medium from flowing back into the parenchymal venous branches so that it is available to fill the anastomotic branches.

We cannot exclude the possibility that the characteristic phlebographic pattern of hydronephrosis reflects, at least in part, a pre-existing modification in blood flow distribution. This view is supported by experimental studies that indicate an enhanced blood flow in the outer cortex and a reduced blood flow in the juxtamedullary cortex and medulla secondary to an increased intrapelvic pressure (Carlson and Sparks, 1970).

The fine network observed in 4 cases of hydronephrosis in an advanced stage could be due both to a reduced intraparenchymal venous pressure, secondary to a decreased endopelvic pressure, and to a reduced renal blood flow that allow an extensive back flow of contrast medium. This hypothesis is supported in this case by surgical evidence showing poor vitality of the renal parenchyma associated with the presence of the fine network. However, we have observed that this fine network is not characteristic of hydronephrosis in an advanced stage, but has been encountered in other conditions associated with extensive lesions of the renal parenchymal tissue.

When the branches of the renal vein are not visualised it is a sign of disruption by secondary infection of a hydronephrotic kidney and is associated with an occlusion of the renal artery. However, it must be kept in mind that in rare instances the back flow of contrast medium injected through the catheter in the renal vein may also be prevented by competent venous valves. (Fig. 5).

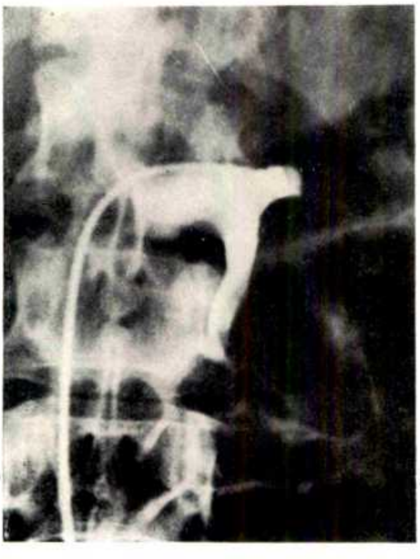


Fig. 5. Left renal phlebography of a normal kidney. There is a competent venous valve that prevents further progression of the catheter and a reflux of contrast medium in the distal portion of the vein. Visualisation of the superior end of the left gonadic vein.

In 3 patients, where both arteriographic and phlebographic investigations were performed, the alterations of the phlebographic pattern were more obvious, indicating a more marked alteration of venous blood flow in hydronephrosis. This confirms what has been observed in hydronephrosis produced experimentally in rabbits where an early effect is extensive congestion of the venous system (Rao and Heptinstall, 1968), suggesting that venous system disturbances play an important role in the development of the renal atrophy in hydronephrosis.

Although experience with phlebography in hydronephrosis is limited, this procedure may be preferable to urography and arteriography in defining the state of renal parenchyma.

Summary

A phlebographic study of the renal venous tree was made in 24 cases of hydronephrosis. There was an alteration in the renal phlebographic pattern, the most characteristic appearance being the visualisation of extensive free anastomoses among the branches of the renal vein.

Elongation of the branches of the renal vein, which is not as typical nor as constant, is presumably caused by enlargement of the pelvis and the distended calyces. In more advanced stages there is a visualisation of a fine network located peripherally to the previously described anastomoses. When there is a secondary disruption of the renal parenchyma there is no visualisation of the branches of the renal vein.

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The Author

Fabio Floris, MD, First Assistant, Department of Urology, University of Trieste, Italy.

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123-Iodine: a New Isotope for Functional Renal Scanning

P. H. O'REILLY, K. J. HERMAN, R. S. LAWSON, R. A. SHIELDS, and H. J. TESTA
Departments of Urology, Medical Physics and Nuclear Medicine, Manchester Royal Infirmary, Manchester

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In recent years, the clinical urologist has had available the benefits of radionuclides in the investigation of diseases of the kidneys and urinary tract. Several tests have been developed, including the radioisotope renogram for the assessment of renal function, and renal "scanning" for the evaluation of renal morphology. Early problems in renography of low renal clearance or extrarenal accumulation of the radiopharmaceuticals were overcome by the introduction of 131-I-orthoiodohippurate (Hippuran) (Tubis, Posnick and Nordyke, 1960) with its high renal extraction and rapid transit time. Similarly, the use of radiotoxic mercurial compounds for renal imaging has been replaced by the newer 99m-technetium labelled pharmaceuticals such as diethylenetriaminepentaacetic acid (DTPA) (Hauser, *et al.*, 1970), gluconate (Boyd *et al.*, 1973) and 2-3-dimercaptosuccinic acid (DMSA) (Englander, Weber and Dos Remedios, 1974). These agents have brought radionuclide imaging to a high degree of morphological definition and, using the gamma camera in conjunction with digital computer systems, have introduced possibilities of quantitative assessment of individual renal blood flow and function.

The routine practice in this department has been to investigate urological problems by 131-I-Hippuran renography and 99m-technetium DTPA imaging with both dynamic and static studies. We have recently, however, had the opportunity to assess the clinical potential of 123-iodine in the field of urological practice. 123-iodine is a cyclotron-produced isotope emitting gamma rays of energy 159 keV and having a half-life of 13·3 hours. These excellent physical characteristics permit the production of renal images of high resolution whilst delivering a low radiation dose to the patient. The 123-I used in this trial was of high radionuclidic purity and was supplied by A.E.R.E., Harwell.

Materials and Methods

The 123-I-Hippuran was prepared by a slight modification of the fusion method described by Thakur, Chauser and Hudson (1975). Initially, the 123-I received as sodium iodide in sodium hydroxide solution, was transferred to a 15 ml conical centrifuge tube; the pH was adjusted to 8 before reducing the volume to 0·5-1·0 ml by boiling, in order to minimise hydrolysis. 100 mg of orthoiodohippuric acid was dissolved in 1·0 ml of ethanol and transferred to the 123-I solution; this solution was then evaporated on a silicone oil bath at 178°-185°C using a nitrogen bleed; a viscous melt was obtained which was maintained for 1 min before removing the tube from the bath. The tube was then cooled and 1·5 ml of 3 M NaOH added to dissolve the melt.

The solution was then further cooled in a salt-ice bath before the addition of 0·5 ml 10 M HCl which precipitated the Hippuran. The precipitate was then centrifuged and the supernatant liquor removed before washing with 1·0 ml portions of ice-cold, pyrogen-free water. The precipitate was redissolved in 0·3 M NaOH and the pH adjusted to 7 with 0·1 M HCl. The solution was then withdrawn and passed through a 0·22 μm membrane filter into a sterile serum vial. Quality control was initially performed using a Gelman silica thin-layer chromatography plate, eluting with

Table I

Diagnostic Analysis of Cases investigated with 123-I-Hippuran.

Case	Initial complaint	Radiological diagnosis	Radioisotope diagnosis	Final diagnosis
1 Fig. 3.	RIF pain, ?renal colic	Bilat. hydronephrosis, lower ureters not seen, ?lower ureteric calculi	Bilat. hydronephrosis, bilat. hydroureter to V/U junction. Obstruction	Bilat. obstructing lower ureteric calculi
2	L-renal colic	Staghorn calculus in L kidney, ?absent R kidney	Pelvi-calyceal filling defect (stone) in single left kidney	Staghorn calculus, solitary L kidney
3	R-loin pain	S.O.L. R kidney, ?nature. Angiography = carcinoma	S.O.L. R kidney, ?nature, 1st circulation not available	Hypernephroma
4 Fig. 5	L-loin pain	S.O.L. both kidneys, esp R, ?nature, ?cysts. Angiography = cysts	Polycystic disease	Polycystic disease
5	Hypertension	R kidney normal, L kidney small	R kidney normal. Small poorly perfused L kidney	End-stage obstructive-uropathy
6	L-loin pain	No IVU	Delayed uptake and excretion on R, ?hydroureter	Pending
7	L-loin pain	L duplex system but no other abnormality	Unequal perfusion—very poor on L. Small L-kidney area with normal function	Pyelonephritis in duplex system?
8 Fig. 1	Bilat. loin pains	Iodine hypersensitivity	Normal appearances	
9	Hypertension	Distension R renal pelvis. Kinked upper R ureter	R renal pelvis obstruction, very poor drainage.	Pelvi-ureteric obs.
10 Fig. 4	Previous bilat. calculi, R-loin pain	Bilat. mega-ureter and megacalycosis, no stones	Mega-ureter and calycosis. Poor drainage from R-renal pelvis especially	Congenital
11	L-loin pain, haematuria	Normal appearances.	R kidney much smaller than L. Poor right perfusion	Auto erythrocyte sensitisation syndrome

S.O.L. = space occupying lesion.

Table II

Comparative Radiation Dose (rad/mCi) due to 131-I and 123-I-Hippuran in Renal Scanning

Isotope	Kidney	Bladder wall	Thyroid	Whole body	Gonads
131-I	0·1-0·6	0·7-3·1	17	0·02-0·1	0·02-0·1
Pure 123-I*	0·03-0·1	0·2-0·6	0·16	0·004-0·02	0·005-0·04
Impure 123-I†	0·04-0·1	0·2-0·8	0·80	0·005-0·03	0·006-0·05

* Including less than 0·2% 125-I and negligible 124-I and 126-I.
† Including 4% 124-I, 0·9% 125-I and 0·5% 126-I.

Table III

Hippuran Clearance Parameters used in Radiation Dosimetry Calculations

	Normal function	Poor function
K_{13}	0·03 min^{-1}	0·03 min^{-1}
K_{31}	0·05 min^{-1}	0·05 min^{-1}
K_{12}	0·04 min^{-1}	0·004 min^{-1}
t_0	5 min	20 min
t_v	1 hr	5 hr

For explanation of symbols see text.

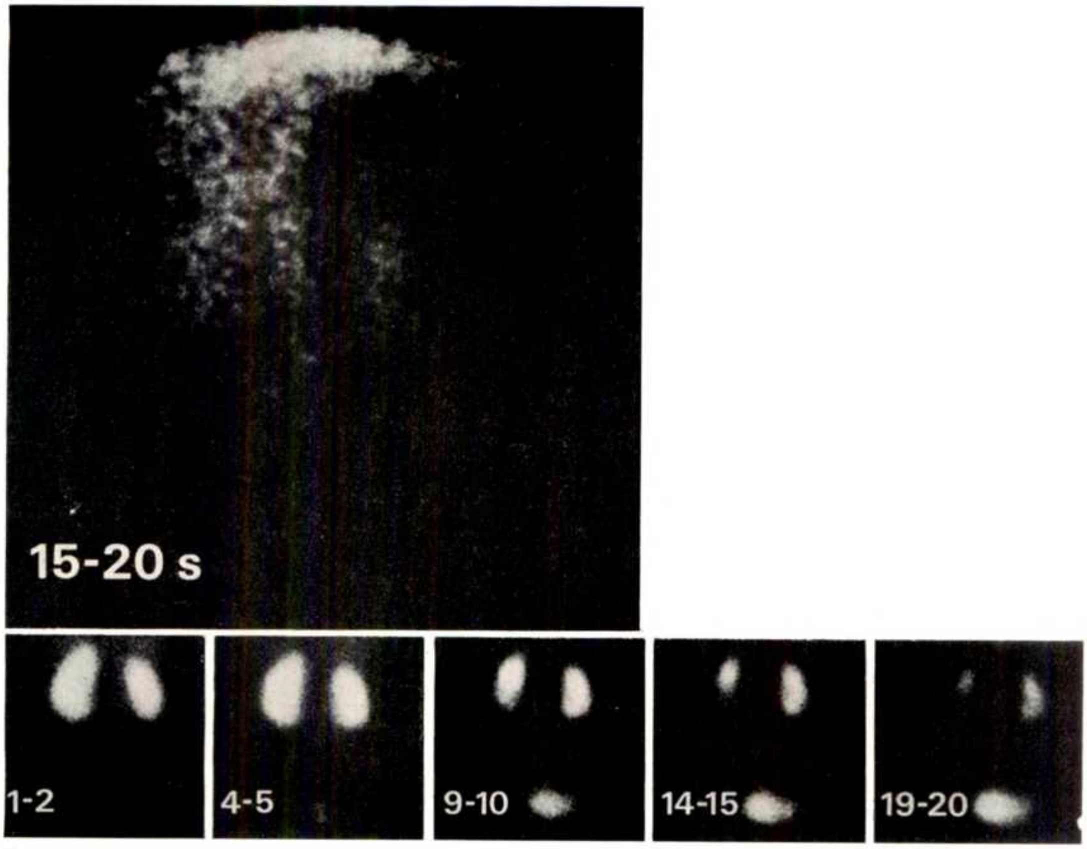

Fig. 1. (a) Dynamic; (b) Static scintiscans from normal patient (case 8, Table I).

9 : 1 chloroform; glacial acetic acid; Rf Hippuran = 100; Rf iodide = 10. The amount of free iodide present was found to be between 0·2 and 1%.

Procedure

11 patients from the urological clinic underwent investigation. A dose of 1 to 2 millicuries of 123-I-Hippuran was injected intravenously and subsequent renal images produced using a gamma camera on-line to a digital computer (either Nuclear Enterprises Mk III with Digital Equipment Co. PDP-12 computer, or General Electric Radicamera with Med II system). Analog pictures were obtained using 1-min exposures at 2, 5, 10, 15 and 20 min after injection and, at the same time, the information was digitised on a 64 × 64 matrix and stored in 2-min frames for a total time of 30 min. Renograms were produced using the computer stored data and defining the region of each kidney with a light pen. In a group of selected patients, first circulation pictures were obtained by giving a flushed bolus injection of 4-8 millicuries of 123-I-Hippuran and storing 1 sec frames between 10 and 40 sec.

Cases and Results

5 men and 6 women between the ages of 28 and 69 years were studied. All were in a good state of hydration and were scanned in the sitting position. All had a complete urological work-up in-

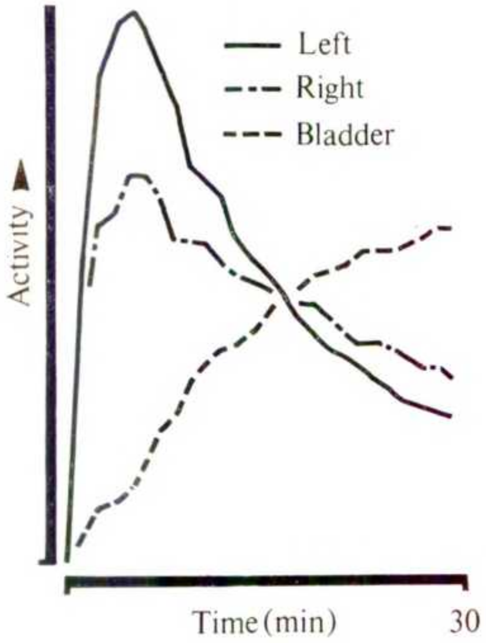

Fig. 2. Computer-derived renogram from patient in Fig. 1 showing normal appearances.

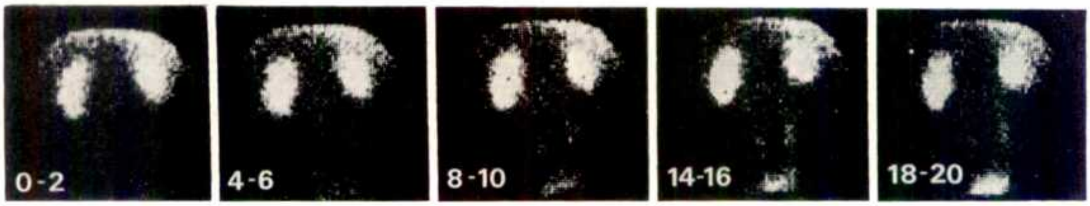

Fig. 3. Static scintiscans from patient with bilateral obstructing lower ureteric calculi (case **1**, Table I).

cluding full biochemical profile, intravenous urography (excepting 2 cases), cystoscopy and 131-I-Hippuran renography. 2 patients had selective renal angiography. There were no paediatric or uraemic patients in the group. Table I shows the presenting complaint and the radiological, radioisotope and where possible, clinicopathological diagnosis. Examples of dynamic and static scintiscans plus an example of the computer-derived renogram appear in Figures 1 to 5.

Radiation Dosimetry

The radiation dose to the patient from the administration of 123-I-Hippuran has been calculated and compared with that due to 131-I-Hippuran. Table II shows the range of radiation dose which would be absorbed by different organs after the administration of 1 mCi of each radiopharmaceutical. The lower figure in each case applies to a patient with normal renal function and the higher figure to a patient with poor renal function.

The dose absorbed by various organs per unit of cumulated activity in the kidneys, bladder, thyroid and total body tissue has been taken from the tables calculated by the Medical Internal Radiation Dose Committee (Snyder *et al.*, 1975) and assumes a uniform distribution of activity within each of these organs. The cumulated activity in

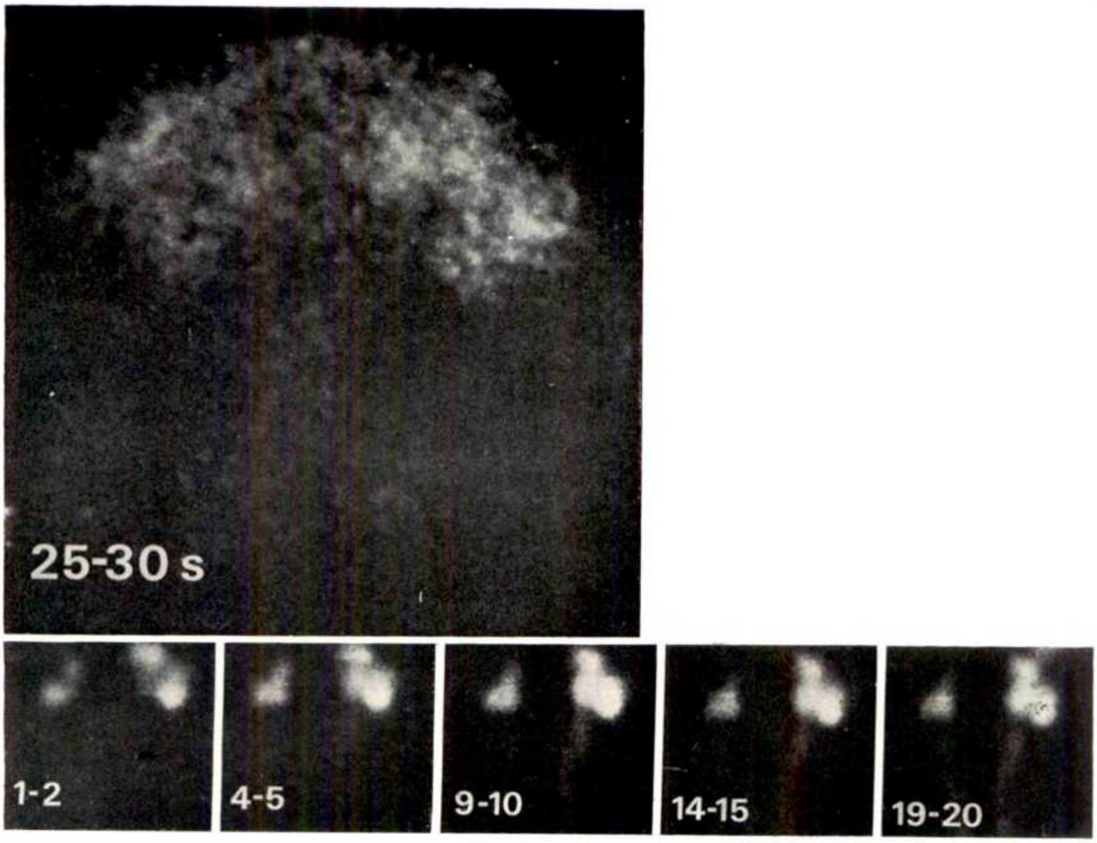

Fig. 4. (a) Dynamic; (b) Static scintiscans from patient with bilateral megaureter and megacalycosis (case 10, Table I).

kidneys, bladder and body tissue has been calculated using a 3-compartment model for Hippuran clearance (Blaufox, 1972). In this model Hippuran is injected into compartment 1 (blood plasma) and diffuses into compartment 3 (extravascular space) with a rate constant K_{13}. Diffusion also takes place in the reverse direction with a rate constant K_{31}. Uptake from blood plasma to kidney is represented by a rate constant K_{12} and after a transit time t_0 through the kidney Hippuran enters the bladder which is voided at a time t_v after injection. The values assumed for these parameters for both normal and poorly functioning kidneys are shown in Table III. The values of the rate constants are based on measurements of Hippuran clearance by Blaufox (Blaufox, 1972). The cumulated activity in the thyroid has been calculated on the assumption of 1% free iodide in the Hippuran, 30% uptake by the thyroid with a half-time of 6 hours and negligible biological elimination.

The contribution to the radiation dose from isotopic impurities is negligible for the pure isotope that we have used but other methods of production can give significant 124-I contamination (Short *et al.*, 1973) and this has a particularly important effect on the radiation dose to the unblocked thyroid.

If 131-I-Hippuran is used the thyroid is the critical organ, but use of pure 123-I-Hippuran with its much shorter half-life and reduced β emission reduces the radiation dose to the thyroid by a factor of 100 and to the kidneys and bladder by a factor of approximately 5. In this case the bladder is the critical organ and the radiation dose can be reduced by earlier voiding.

Discussion

An overall feature in all cases was the impressive clarity of the resultant images, both in the early transient parenchymal phase and in the collecting systems. This is well shown in Figure 1 which demonstrates normal appearances in dynamic and static phases plus the corresponding normal computer-derived renogram (Fig. 2). In some cases, excretion of the tracer from renal calyces and pelvis was seen with subsequent progress down morphologically well-defined ureters; this is well illustrated by Figure 3 (case 1 in Table I) where ureteric visualisation led to the diagnosis of bilateral ureteric obstruction due to calculi at the vesico-ureteric junction; the ureters had not been seen adequately on the IVU available at that time, and the radioisotope findings led to the institution of immediate corrective measures. Similar ureteric definition was achieved in case 10 whose scans are shown in Figure 4. This patient presented with right-loin pain and was found to have bilateral mega-ureter and megacalycosis with impaired drainage from the right collecting system. In patient 4, Figure 5, the previous IVU examination had shown space-occupying lesions affecting both kidneys, especially the right; the renal scan led to the firm diagnosis of polycystic disease, and this was later confirmed by arteriography.

The use of this isotope has a significant advantage: it permits by the single injection of a single radiopharmaceutical, visualisation and analysis of the first circulation with later static pictures of the concentration and excretion of the Hippuran, all using a non-invasive test lasting a period of perhaps 30 min. Furthermore, this high resolution scanning is accomplished with only a low radiation dose to the patient. The 123-I isotope will thus have an added attraction for use in paediatric urology, in cases where regular periodic follow-up is necessary (*e.g.* renal homografts, obstructive states, urodynamics) and in patients with renal failure. It has already been used successfully in the calculation of Effective Renal Plasma Flow (Chisholm, Short and Glass, 1974),

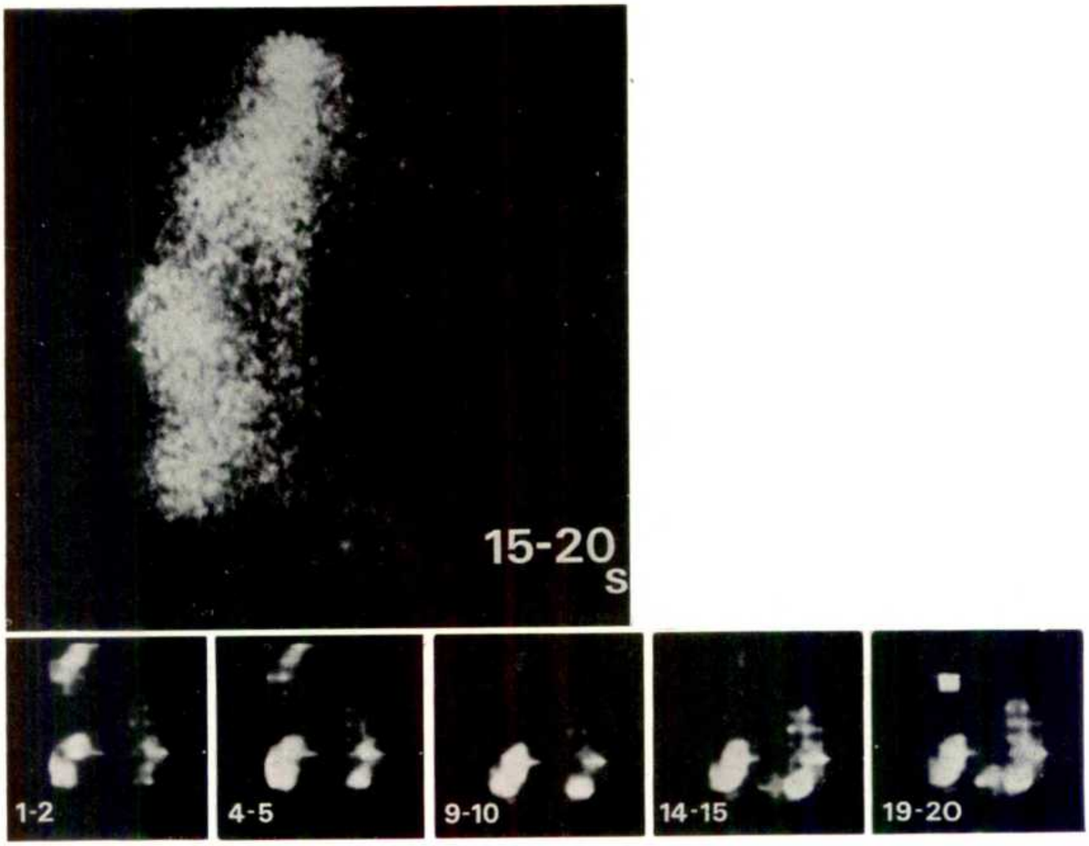

Fig. 5. (a) Dynamic; (b) Static scintiscans from patient with polycystic disease (case 4, Table I).

and preliminary work on deconvolution renography has been reported (Fleming *et al.*, 1975). The biggest single disadvantage of this isotope is its expense; it is, in fact, not currently available in the pure form for routine application. One hopes that this will not mitigate against the full evaluation of its promising potential.

Summary

The results are presented of functional renal scanning in 11 urological patients using 123-iodine labelled Hippuran—a new radiopharmaceutical.

The 123-iodine isotope possesses distinct advantages over existing isotopes, permitting high resolution imaging whilst delivering a low integrated radiation dose.

It is hoped that the expense of this cyclotron-produced isotope will not mitigate against full evaluation of its promising potential.

Our thanks are due to Mr E. Charlton-Edwards and Mr R. N. P. Carroll for their co-operation and assistance.

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The Authors

P. H. O'Reilly, FRCS, Urological Research Fellow.
K. J. Herman, MRIC, Chief Technician.
R. S. Lawson, PhD, Physicist.
R. A. Shields, MSc, Principal Physicist.
H. J. Testa, PhD, Consultant in Nuclear Medicine.

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Short Case Report

Percutaneous Diagnosis and Treatment of Intra-renal Abscess

Case Report

A 36-year-old nurse had antibiotic treatment for an *E. coli* urinary infection. She had severe pain radiating from the right loin to the right shoulder. Chest X-rays and I.V.P. were taken 2 weeks later. There was right basal collapse with a markedly raised hemi-diaphragm. A right renal mass lesion was present (Fig. 1). The combination suggested an infected cyst, and at "cyst" puncture 120 ml of foul-smelling greenish-yellow pus was aspirated. Contrast medium showed "tracking" outside the "cyst" (Fig. 2). Ampicillin and streptomycin was injected into the "cyst" and she was restarted on Septrin. *E. coli* was found in the pus. Repeat I.V.P.s in April and October 1974 showed progressive reduction in size of the "cyst" and in September 1975 it was no longer visible.

Comment

This patient was treated solely as an outpatient. The abscess was diagnosed, washed out and treated by a single "cyst puncture" and antibiotics. The iodine contrast agent not only demonstrated the confines of the abscess but also had a sterilising effect, as has been shown experimentally *in vitro* (Jacot and Modde, 1973) and in other cases the author has seen, a notable one being an intrahepatic abscess which had drained for a year and then healed. A previous report of percutaneous treatment of intra-renal abscess (by an indwelling catheter) is by Stables and Jackson (1974).

F. W. WRIGHT
Department of Radiology, Churchill Hospital, Oxford, OX3 7LJ

JACOT, C. and MODDE, H. K. (1973). In vitro studies on anti-bacterial potency of radiological contrast media. XIII International Congress of Radiology, Madrid. Excerpta Medica No. 301, 3.

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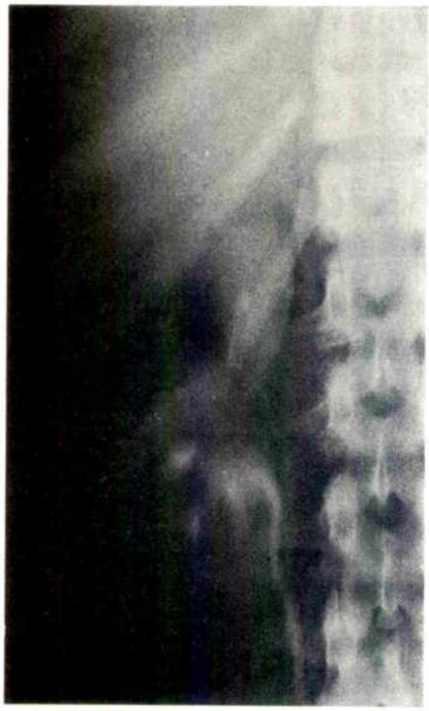

Fig. 1. I.V.P. tomogram (Jan. 1974). Large mass in the upper pole of the right kidney—fairly well-defined intrarenally, but outer aspect ill-defined. *Note:* the duplex collecting system bilaterally.

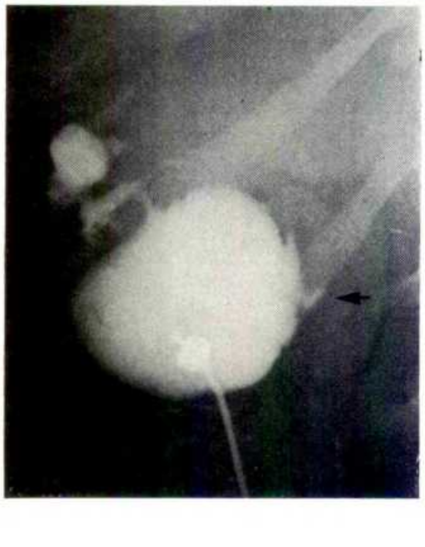

Fig. 2. (Two weeks later.) Renal "cyst" puncture — leakage of contrast medium is shown from the abscess or infected cyst mainly superiorly, but a little also into the medial aspect of the kidney (arrowed).

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Primary Malignant Lymphoma of the Testis associated with Sclerosis and Nodularity

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A. TALERMAN
Department of Pathology, Institute of Radiotherapy, Postbus 5201, Rotterdam, The Netherlands

Primary malignant lymphoma of the testis was first described by Malassez in 1877. Although in the subsequent 70 years this entity has received little attention, during the last 3 decades it has been subject to a number of reports and reviews (Gowing, 1976).

Primary malignant lymphoma of the testis, unlike testicular neoplasms of germ cell origin, usually affects men older than 50 years, and is the most common testicular neoplasm in elderly males (Abell and Holtz, 1968). This tumour is generally associated with a poor prognosis, frequently involves both testes, although usually not at the same time, and is often followed by generalised involvement of lymph nodes and extranodal sites by the disease, although the development of leukaemic blood picture is rare (Gowing, 1976).

During a review of cases of primary malignant lymphoma of the testis a case showing an unusual histological pattern, and associated with 5-year survival was encountered.

Case Report

A 21-year-old male noted enlargement of the right half of the scrotum in January 1971 following minor trauma. The mass was slightly tender, and showed progressive enlargement. The patient was seen by a urologist in March 1971 who diagnosed a hydrocoele and advised surgical treatment.

At operation it was noted that the hydrocoele fluid was haemorrhagic and that the testis was enlarged, hard and had irregular contour. There was also enlargement of the epididymis, which was firm and slightly nodular. Biopsies were taken from the testis and epididymis and a malignant neoplasm was diagnosed on frozen section. Radical orchidectomy was performed. The postoperative recovery was uneventful. The tumour was originally diagnosed as a classical seminoma with marked fibrosis and hyalinisation. The patient was referred for further investigations and treatment. Haematological and biochemical investigations revealed no abnormalities. The chest X-ray was normal. Lymphangiography revealed enlargement of para-iliac and para-aortic lymph nodes on the right side, and possibly some abnormalities on the left side. There was no enlargement of other lymph node groups, spleen or liver. The patient was treated with radiotherapy and 3,000 rads were administered to the iliac and the para-aortic lymph nodes and 1,600 rads to the right side of the scrotum during April and May 1971. The histological diagnosis was in the meantime revised to that of malignant lymphoma of the testis. Since then the patient has been followed in an outpatient clinic. He was well and symptom free when last seen in April 1976 5 years after the orchidectomy.

Pathology

The radical orchidectomy specimen consisted of a testis measuring 8 × 6 × 5 cm with an epididymis measuring 5 cm and a segment of spermatic cord measuring 8 cm. The testis was firm to hard, uniformly grey-yellow with a somewhat irregular contour. The epididymis was enlarged forming an oval mass 3 cm across at the upper pole. A small tumour nodule 0·3 cm across was present within the spermatic cord. On cross-section the tumour showed uniform appearances (Fig. 1). It was grey-yellow in colour and showed a somewhat nodular or lobulated pattern. The tumour replaced nearly the whole testis, but in a few places normal testicular tissue was still discernible (Fig. 1). There was invasion of the tunica albuginea by the tumour in many places. Microscopically the lobular or nodular pattern was evident (Fig. 2), and cellular tumour nodules were

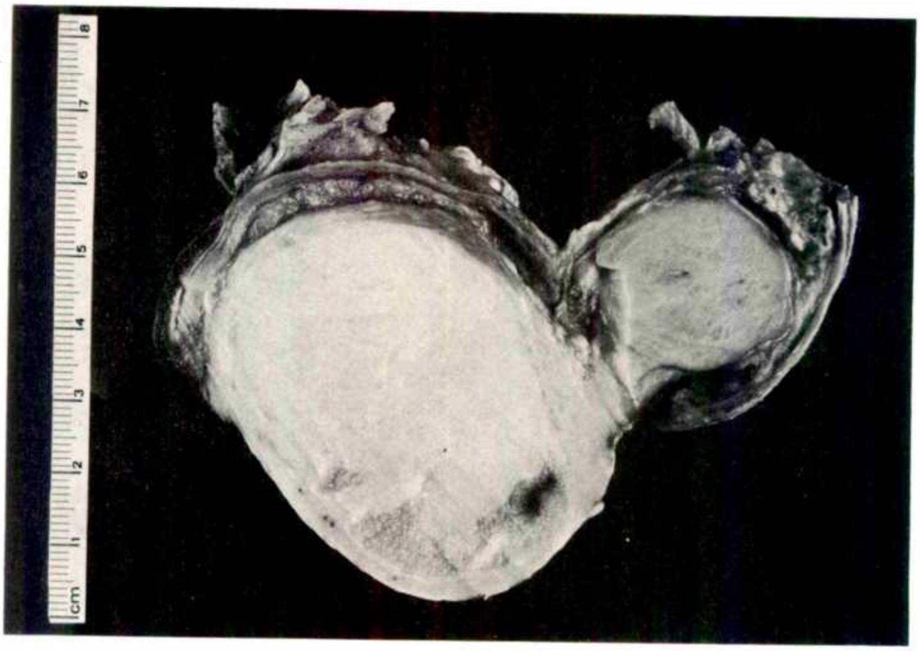

Fig. 1. Hemisection of the enlarged right testis and epididymis nearly completely replaced by the tumour.

intersected and separated by bands of amorphous collagenous tissue. Nodules composed of hyalinised tissue containing atrophic seminiferous tubules were also evident (Figs. 2 and 3).

In the cellular areas the tumour cells formed large aggregates and either effaced completely the normal testicular architecture or surrounded and widely separated normal sized although atrophic seminiferous tubules (Fig 3). This was even more evident in sections stained to demonstrate reticulin fibres. There was an increase in reticulin fibres, which surrounded individual tumour cells, and formed a network around the seminiferous tubules (Fig. 4). The tumour cells were medium sized with round, or oval hyperchromatic or slightly vesicular nuclei and a narrow rim of cytoplasm (Fig. 5). There was brisk mitotic activity. The bands of collagen separating the nodules were acellular, but contained atrophic seminiferous tubules (Fig. 3). The epididymis was nearly completely replaced by the tumour. There was widespread invasion and in places penetration of the tunica albuginea. The tumour was seen to invade some blood vessel walls, and was present in lymphatic vessels. The nodule from the spermatic cord was composed of tumour tissue. The resection margin of the spermatic cord was free from tumour deposits.

The appearances were those of malignant lymphoma of the testis with a nodular pattern and an unusual degree of sclerosis.

Discussion

Primary malignant lymphoma of the testis is uncommon comprising approximately 7% of testicular neoplasms (Pugh, 1976).

The diagnosis is based upon the testicular enlargement being the first and main presenting symptom or sign, and on the absence of previous involvement by malignant lymphoma. This entity must be differentiated from the involvement of the testis by a generalised malignant lymphoma, or by leukaemic infiltration, which are by no means uncommon especially in the

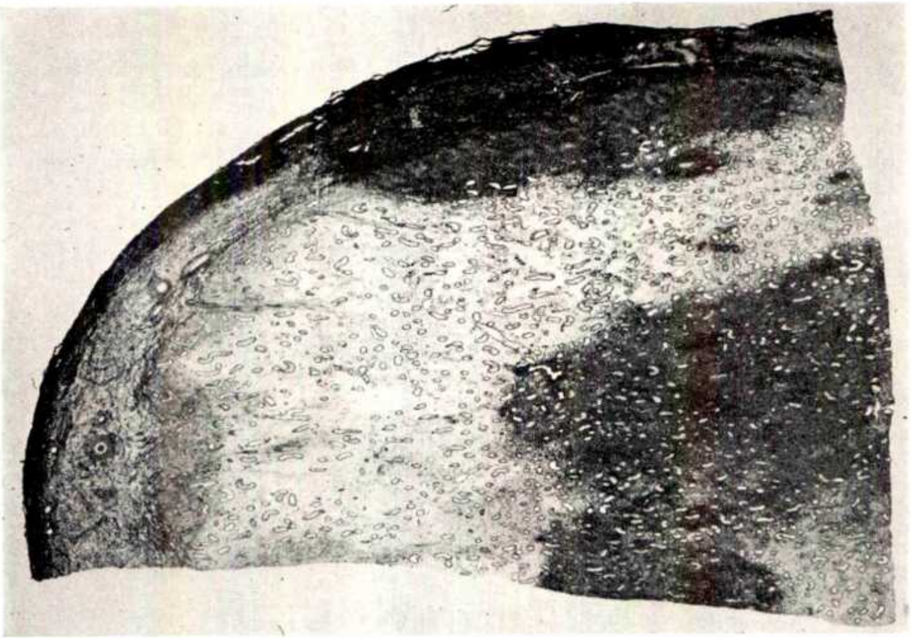

Fig. 2. The testicular tumour showing sclerosis and nodularity. Note the dark areas densely infiltrated by the tumour and the adjacent pale hyalinised areas containing atrophic seminiferous tubules. (H & E. × 7.)

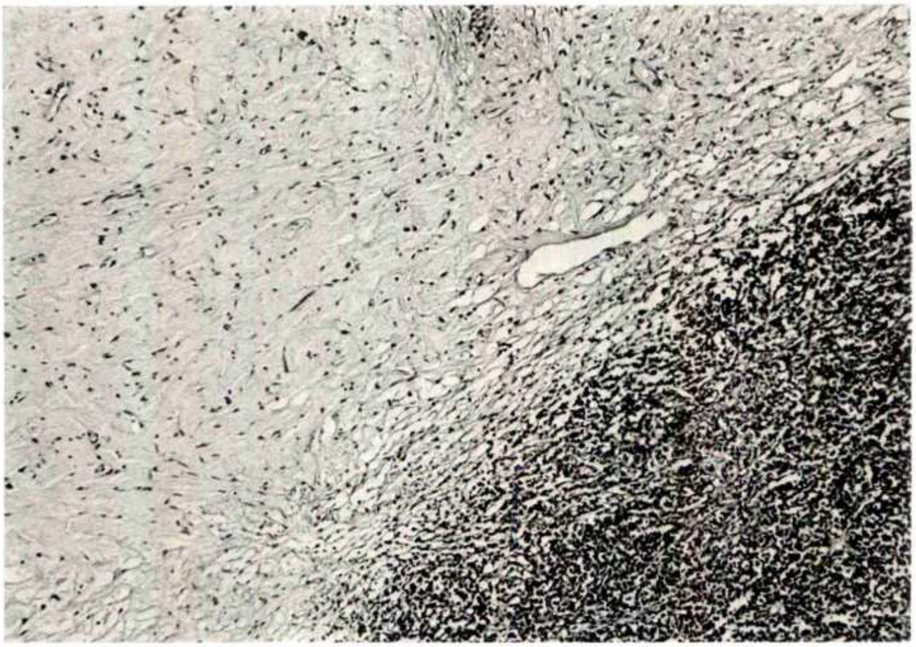

Fig. 3. Histological appearances of the tumour showing the edge of tumour nodule and a densely hyalinised area. (H & E. × 150.)

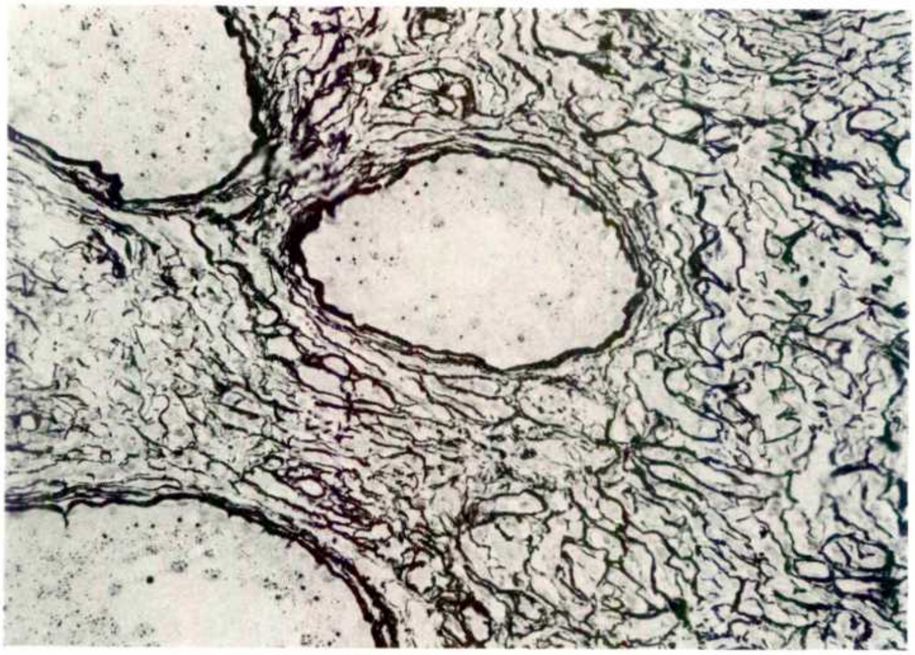

Fig. 4. The network of fine reticulin fibres present around individual tumour cells and surrounding concentrically seminiferous tubules. (Gomori's reticulin stain. × 380.)

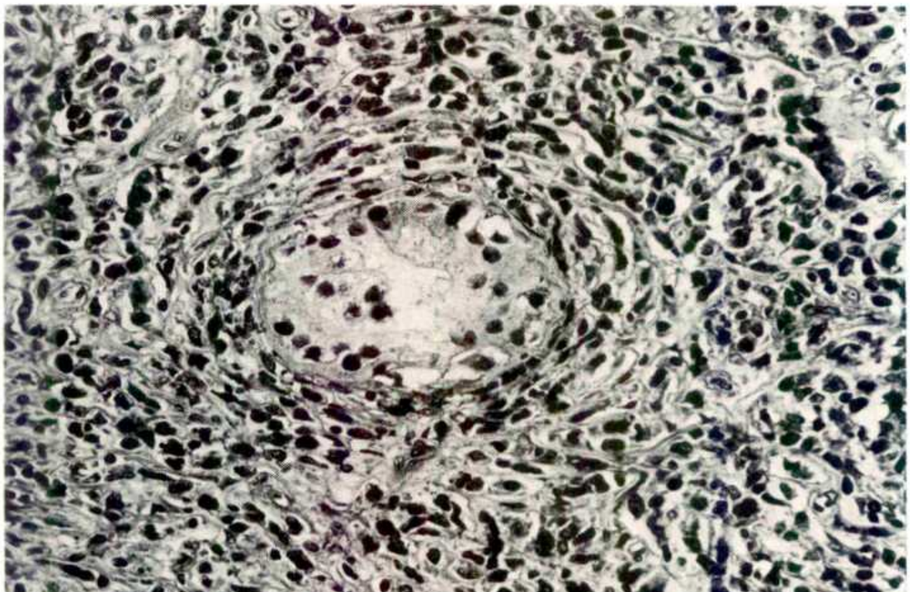

Fig. 5. Histological appearances of the tumour cells surrounding a seminiferous tubule. (H & E. × 380.)

terminal stages of these diseases. Review of 32 cases of primary malignant lymphoma of the testis, diagnosed using the above-mentioned criteria, seen in this institution and in consultation revealed that the present case differed as regards the histological picture, age and survival. The presence of marked hyalinisation, fibrosis and nodularity has not been previously recorded in descriptions of malignant lymphoma of the testis, and was not noted in the large series studied by the British Testicular Tumour Panel (Gowing, 1975).

The unusual amount of fibrosis and hyalinisation suggested that the tumour was a seminoma and this was, in fact, the original diagnosis. Seminoma is the testicular tumour most frequently confused with malignant lymphoma (Melicow, 1955; Gowing, 1976) but the histological appearances in the more cellular areas of the present tumour, and in particular reticulin pattern were inconsistent with this diagnosis. The marked sclerosis also raised the possibility that the lesion might not be neoplastic, but a pseudotumour; however examination of the more cellular areas revealed features of malignancy and appearances typical of malignant lymphoma. Nevertheless the possibility that the sclerosis might have been due in part at least to trauma cannot be entirely excluded, though the trauma which led to the discovery of the lesion was of such minor nature that it appears unlikely that it produced such marked changes in so short a period of time.

As most patients with malignant lymphoma of the testis are older than 50 years (Gowing, 1976), the age of the present patient is another unusual feature.

The prognosis with primary malignant lymphoma of the testis is poor and the majority of patients die with generalised disease within 2 years of orchidectomy (Abell and Holtz, 1968; Gowing 1976). 20 of our 24 patients with complete follow-up information died of generalised disease within 2 years of diagnosis.

The possibility that in the present case the marked sclerosis and nodularity represent a favourable prognostic feature must therefore be considered, as it has been shown that nodular sclerosis is associated with better prognosis both in Hodgkin's disease (Lukes, 1963) and in non-Hodgkin lymphoma (Bennett and Millett, 1969: Millett *et al.*, 1969). In the present case there was a favourable outcome in spite of very extensive involvement of the testis including the tunica, epididymis, presence of a tumour nodule within the spermatic cord and lymphangiographic evidence of involvement of the para-iliac and para-aortic lymph nodes.

The absence of further dissemination indicates that the tumour was primary in the testis and as extra-nodal malignant lymphoma has frequently a better prognosis than malignant lymphoma affecting the lymph nodes, differentiation between cases where the tumour affects only the testis and its regional lymph nodes and those showing evidence of more extensive involvement is considered to be of importance as far as therapy and prognosis are concerned.

Summary

A case of primary malignant lymphoma of the testis associated with an unusual degree of sclerosis and nodularity is reported.

The patient, a 21-year-old male, is alive and well 5 years after orchidectomy followed by radiation therapy to the lumbar and para-aortic lymph nodes in spite of very extensive involvement of the testis, epididymis and presence of tumour deposits within the spermatic cord and in para-aortic lymph nodes. It is suggested that sclerosis and nodularity may be favourable prognostic features in patients with primary malignant lymphoma of the testis.

Acknowledgment

I would like to thank Professor N. F. C. Gowing for review of the histology.

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Urodynamic Assessment of Bladder Function

D. J. GRIFFITHS
Department of Physics, University of Exeter, Exeter, Devon

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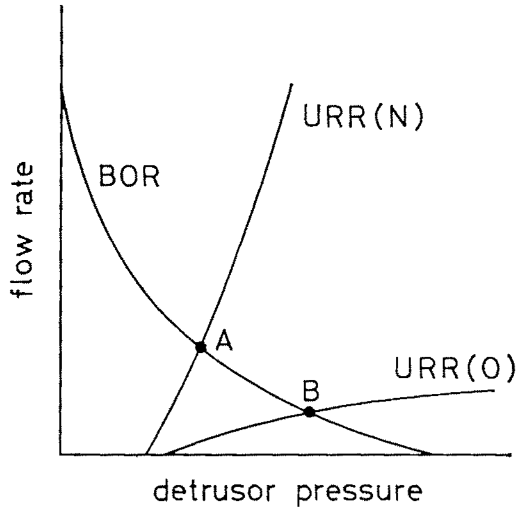
In conventional urodynamic investigations the function of the bladder during voiding is assessed mainly from the detrusor pressure (or intrinsic bladder pressure) at peak flow. This pressure, however, is not a good test of the function of the bladder alone, because it depends also on the properties of the urethra. What is required is a way of obtaining separate information about bladder and urethra from urodynamic data. I have shown previously (Griffiths, 1973) that, if pairs of simultaneously measured values of the flow rate and the detrusor pressure are plotted against one another throughout the course of micturition, a curve is obtained which shows the flow rate that is forced through the urethra by any given detrusor pressure; that is, the curve illustrates graphically the urethral resistance to flow, and so I have called it the "urethral resistance relation". The urethral resistance relations of obstructed and unobstructed urethras are quite distinct, as shown schematically in Figure 1, and may be used in the assessment and understanding of urethral obstruction (Griffiths, 1974; Bates, Arnold and Griffiths, 1975).

Consider now the behaviour of the detrusor. One might think that, with given stimulation and at a given bladder volume, the detrusor pressure would be fixed in value, but this is not so (Griffiths, 1973). The detrusor pressure depends also on the rate of flow of urine out of the bladder (that is, on the speed of shortening of the muscle: a characteristic property of muscle). At zero flow rate the pressure attains its maximum, isometric value. If the flow rate rises the detrusor pressure falls. The flow rate reaches its maximum possible value when the detrusor pressure is approximately zero (Fig. 2). This behaviour resembles that of an electric battery, pressure being analogous to voltage and flow rate to electric current. When a battery is delivering no current, the voltage between its terminals is maximum. While a current is being taken from it, the voltage is lower because of internal resistance: the larger the current, the lower the voltage. The maximum possible current is delivered when the terminals are short-circuited (*i.e.* when the voltage is zero).

I have called the graph of flow rate against detrusor pressure the "bladder output relation" (BOR). Just as the urethral resistance relation is characteristic of urethral function, so the BOR indicates bladder function. Its clinical significance will be examined in this paper.

When a bladder with a given BOR empties through a urethra with a certain urethral resistance relation, the flow rate and detrusor pressure for the 2 parts of the system must obviously be identical. Mathematically this means that the actual values of flow rate and pressure are given by the point of intersection of the 2 relations (Fig. 1). Because of the slope of the BOR, any change in the urethral resistance relation will automatically change not just the flow rate but also the detrusor pressure. For example, as shown in Figure 1, urethral obstruction will raise the pressure (as is commonly seen) without any hypertrophy or change in the degree of activation of the bladder muscle. Only if the BOR itself were altered could one say that there had been a change in bladder function. Thus the BOR allows one to study the bladder with the mechanical influence of the urethra eliminated.



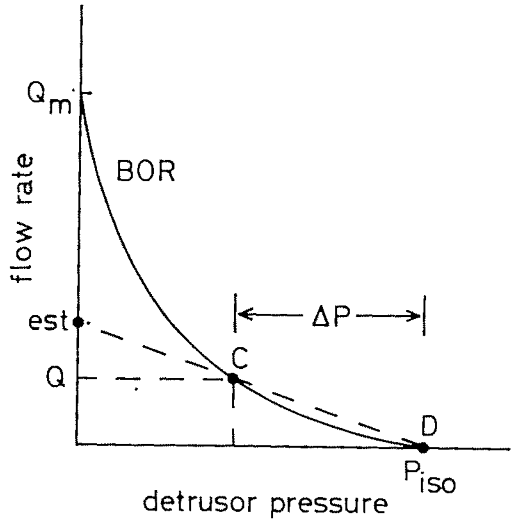


Fig. 1 (*left*). The urethral resistance relation (URR) shows the urine flow rate that can be forced through a given urethra by different detrusor pressures. The bladder output relation (BOR) shows the detrusor pressure that can be generated by a given bladder at different flow rates. The point of intersection (A or B) of the URR and BOR gives the detrusor pressure and flow rate that would be obtained with that bladder and urethra together. Typical URR's for an unobstructed normal urethra (N) and for a proximally obstructed urethra (O) are shown. With the obstructed urethra, not only is the flow rate lower but the detrusor pressure is higher than with the unobstructed urethra, even though the BOR is identical in the 2 cases.

Fig. 2 (*right*). The BOR is defined by the isometric detrusor pressure P_{iso} and the maximum possible flow rate Q_m. During voiding, the URR (not shown) intersects the BOR at a point C and the flow rate is Q. When the external sphincter is shut, the detrusor pressure rises by ΔP to P_{iso} at point D. Q_m may be estimated by extrapolating the line CD back to zero pressure. The intercept on the flow-rate axis is the estimated value (est) of Q_m.

The Bladder Output Relation

The BOR may be defined by two parameters (Fig. 2): the isometric detrusor pressure P_{iso}, which is the detrusor pressure that would be generated if the flow rate were reduced to zero (by shutting the urethra); and the maximum possible flow rate Q_m, which is the flow rate that would (hypothetically) be delivered if the "urethral resistance" could be reduced to zero. Both may be determined if, during micturition and before the bladder is empty, flow is interrupted for a few seconds by the external sphincter. When flow stops, the detrusor pressure rises rapidly to its isometric value (see Fig. 3, and Griffiths, 1973), giving a direct reading of P_{iso}. Q_m is more difficult to measure, but an estimate of it may be obtained either by graphical extrapolation (see Fig. 2) or by calculation (see Appendix sections (*d*) and (*e*)).

The BOR is expected to depend on the volume V in the bladder. Examination of cases where the patient has interrupted the flow more than once during a single micturition has shown that, nearly always, P_{iso} hardly alters as the bladder is emptied, while Q_m (or the estimate of it) decreases (Griffiths, 1974). Further analysis shows that the estimate of Q_m is roughly proportional to $V^{\frac{1}{2}}$ (Griffiths, to be published). Assuming this, one can correct the estimate of Q_m to a standard bladder volume of, say, 200 ml (see Appendix section (*d*)). The corrected, standardised estimate will be given the symbol Q^*. Thus, when voiding is interrupted by use of the external sphincter, P_{iso} may be measured directly and Q^* may be calculated. A simple, rule-of-thumb procedure for this calculation is given in the Appendix, section (*e*).

Although P_{iso} is normally independent of V, it does depend on the degree of activation of the detrusor. For example, when systoles occur without leakage in a neuropathic bladder, then the varying detrusor pressure *is* P_{iso}. Thus gross variations of P_{iso}, if they occur, indicate changes

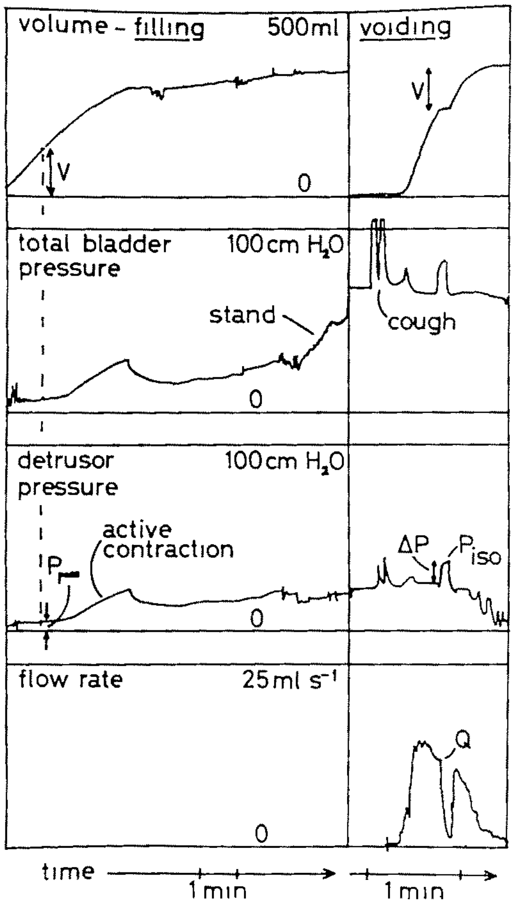


Fig. 3. Tracing of an actual clinical record of the filling of the bladder of a female (age 59) in the supine position and of her subsequent voiding in the erect position. The bladder was filled with 350 ml of X-ray contrast medium and the same volume was voided. During filling some active contraction of the (unstable) bladder occurred. On standing the total bladder pressure rose, but the detrusor pressure (*i.e.* total bladder pressure minus abdominal pressure) remained approximately constant. A cough produced very large spikes in the total bladder pressure, but much attenuated ones in the detrusor pressure, showing that the subtraction of the abdominal pressure was working effectively. During micturition, the external sphincter was shut when the flow rate was Q and a volume V remained in the bladder. The detrusor pressure rose by ΔP to P_{iso}. The detrusor pressure at volume V during filling was P_{pass} and there was at that volume no active contraction of the detrusor.

in the degree of activation. In a few cases it has been possible to calculate Q^* twice during a single micturition at very different levels of P_{iso}, and no significant variation has been noticed (see below). Thus Q^* does not seem to be greatly affected by the degree of activation, and so may be a more stable parameter than P_{iso}.

For a given degree of activation, P_{iso} is the maximum pressure that can be generated by the bladder; that is, it is a measure of the intrinsic strength of the bladder. One would expect it to increase, for example, as a result of hypertrophy. Q^* is a measure of the maximum possible flow rate that the bladder can produce; that is, of the intrinsic speed of the bladder muscle. When normal ranges have been established for these 2 parameters, bladders may be classified as strong or weak, and fast or slow, and pathological significance may be sought.

Method and Material

The urodynamic records of 400 patients consecutively attending a urodynamic clinic have been examined. Although the clinical investigation had not been designed for the present purpose, 123 records (75 male, 48 female) gave usable information about the BOR. The patients have already been assessed from their clinical history, micturating video cystourethrogram and urodynamic findings, using methods which have been described by Bates, Whiteside and Turner Warwick

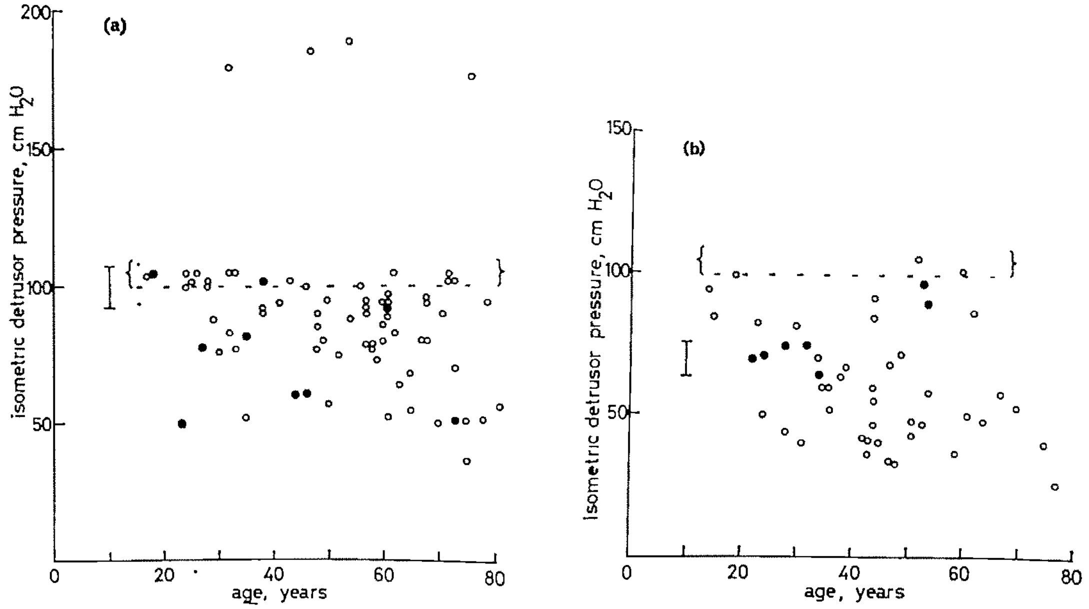


Fig. 4. Dependence of isometric detrusor pressure P_{iso} on age. Values in the bracketed bands above 100 cm H_2O are probably underestimated. ●, normal category (i); ○, all other categories. (a) Males; (b) females.

(1970), Bates (1971), Turner Warwick *et al.* (1973) and Arnold *et al.* (1973). Thus the clinical assessments are the considered collective judgement of an experienced group of workers in the field, and were arrived at quite independently of the results with which they are compared in this paper.

On the basis of the clinical assessment patients have been classified as follows: Males: (i) normal examination, (ii) proximal urethral obstruction, with or without unstable bladder, (iii) post-operation for relief of proximal obstruction, with or without unstable bladder, (iv) unstable bladder not associated with obstruction or primary enuresis, (v) primary enuretic (*i.e.* history of bedwetting persisting after 6 years of age in the absence of infection or of structural or overt neurological abnormality), (vi) other, including doubtful assessments and various types of neuropathic bladder. Females: (i) normal examination, (ii) genuine stress incontinence, (iii) sensory urgency, (iv) unstable bladder not associated with primary enuresis, (v) primary enuretic, (vi) other. The majority of males and females in category (v) have unstable bladders. Some males in this category appear also to be proximally obstructed.

Values of P_{iso} and Q^* have been obtained (see Appendix section (*d*)) for the 123 patients, and have been examined for dependence on sex, age and clinical category.

Results

Reliability and Accuracy

11 of the 123 patients stopped voiding twice during a single micturition, allowing calculation of 2 pairs of values of P_{iso} and Q^*. (Averages have been taken for Figs. 4-6.) In every case but 2 the 2 values of P_{iso} were within 15% of each other.

In these 2 cases, referred to above, the differences were much greater, 54% and 130% respectively. In all 11 cases the 2 values of Q^* were within 35% of each other, even though Q^* is less accurately measured because of the extrapolation and volume-standardisation involved. Thus the estimated errors are usually ±7½% in P_{iso} and

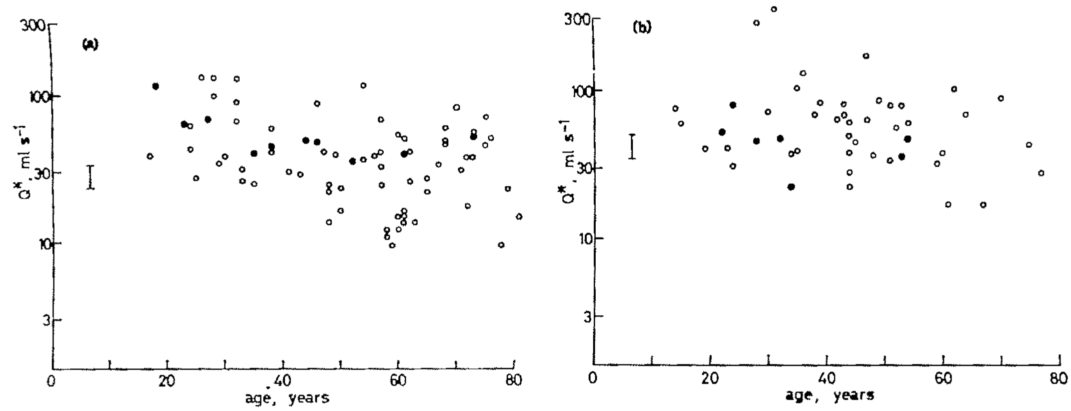


Fig. 5. Dependence of standardised maximum possible flow rate Q^* on age. ●, normal category (i), ○, all other categories. (a) Males; (b) females.

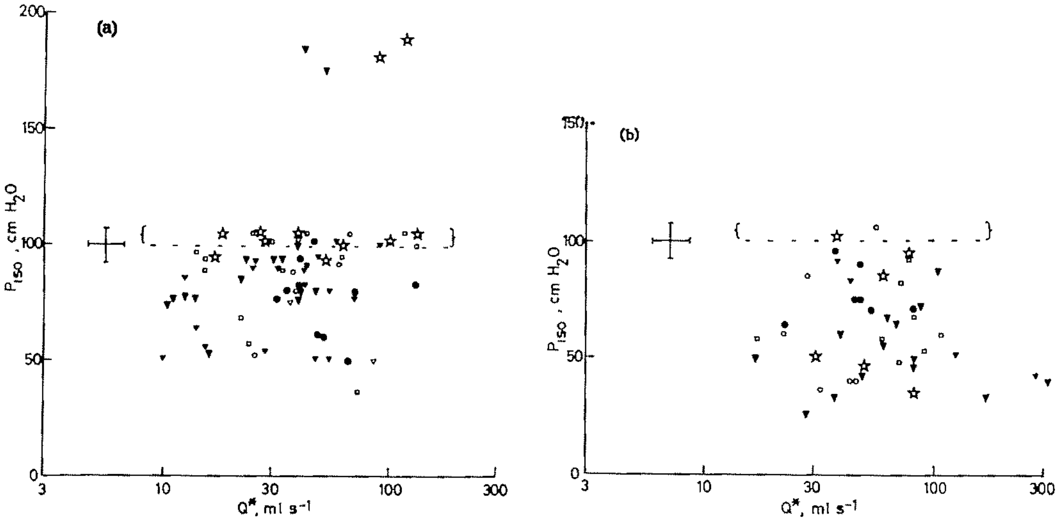


Fig. 6. (a) Dependence of isometric detrusor pressure P_{iso} and standardised maximum possible flow rate Q^* on clinical category in males. ●, normal category (i); ▼, proximal obstruction category (ii); ▽, post-obstruction category (iii); ○, unstable bladder category (iv); ☆, primary enuretic category (v); □, other category (vi). There are significant differences between the mean values of P_{iso} for the primary enuretic and normal categories ($P < 0·005$ by the *t-test*), the mean values of Q^* for the proximally obstructed and normal categories ($P < 0·005$). (b) Dependence of P_{iso} and Q^* on clinical category in females. ●, normal category (i); ▼, stress incontinence category (ii); ▽, sensory urgency category (iii), ○, unstable bladder category (iv); ☆, primary enuretic category (v), □, other category (vi). There are barely significant differences between the mean values of P_{iso} for the normal and stress incontinence categories ($P < 0·025$), and between the mean values of P_{iso} for the normal category and for all the non-normal categories combined ($P < 0·05$).

±17½% in Q^*, as shown on Figures 4-6. Unfortunately, some values of P_{iso} were over 100 cm H_2O, which is off-scale with the normal sensitivity of the apparatus. Therefore they are underestimated at 100(+) cm H_2O. However, the underestimate is not usually very great, because if the detrusor pressure *during flow* is over 100 cm H_2O, the sensitivity is halved and P_{iso} is recorded correctly. Thus the values of P_{iso} in the bracketed band just above 100 cm H_2O in Figures 4 and 6 should lie in the gap between 100 and 170 cm H_2O. The corresponding values of Q^* will also be in error, but not by enough significantly to affect the conclusions.

Isometric Detrusor Pressure P_{iso}

Figure 4, a and b, shows P_{iso} plotted against age for males and females. There is no evidence that P_{iso} depends significantly on age in either sex, especially when normals alone are considered.

Thus, perhaps contrary to expectation, the strength of the bladder does not seem to decline with age.

If category (i) only is looked at, the normal range of P_{iso} seems remarkably similar in males and females, and is from about 50 to perhaps a little over 100 cm H_2O in both sexes, independent of age. When all categories are included, the picture is a little different, because some males have exceptionally strong bladders, while many female patients have bladders which are weaker than normal.

Standardised Estimate of Maximum Possible Flow Rate Q*

Figure 5, a and b, shows that Q^* decreases slightly with age, especially in males, although here the decrease is not really apparent in the normal category (i), but is due to a group of non-normal older males with slow bladders (see below).

The ranges in category (i) are similar for both sexes, being from about 35 to 120 ml s^{-1} in males and 20 to 80 ml s^{-1} in females. These normal ranges are rather broad, and further work may perhaps show that they are over-generous.

Dependence of P_{iso} *and* Q* *on Clinical Category*

Males. Figure 6a shows P_{iso} and Q^* for all the male patients. 2 groups stand out as having bladders different from those in the normal category (i).

There is a group with bladders of slow speed but normal strength. Most of these have, or have had operations to relieve, proximal urethral obstruction (male categories (ii) and (iii)) and are the older patients with slow bladders referred to above.

Another group has bladders of normal speed but of exceptional strength (partly spoilt in Figure 6a by a large number of off-scale readings of isometric pressure). This group contains a high proportion of the primary enuretics, category (v), and a few of the proximally obstructed patients in category (ii).

Females. Figure 6b suggests that a large proportion of all non-normal female patients have abnormally weak bladders of normal speed. A few with stress incontinence or urgency have weak bladders of exceptionally high speed.

Discussion

Males

The majority of proximally obstructed males have bladders of normal strength (normal P_{iso}), and therefore show no mechanical evidence of detrusor hypertrophy, despite the fact that they micturate with a raised detrusor pressure (this being 1 of the criteria for obstruction). Their particular characteristic is a slow bladder (Q^* less than normal). Many, but not all, of those examined after surgical relief or obstruction have similarly slow bladders, perhaps suggesting that urethral obstruction sometimes causes a permanent fall in bladder speed. Schäfer and Melchior (1975), assessing bladder function by a related technique, have reported similar findings in males with prostatic hypertrophy.

A slow bladder tends to produce a low flow rate, whether or not the urethra is obstructed. Therefore it is important to look again at the urodynamic data of these patients to make sure that there is genuine urethral obstruction. This has been done by plotting their urethral resistance relations, which in the great majority are of the obstructed pattern (see Fig. 1, and Griffiths, 1974), although 1 or 2 appear to be unobstructed.

In contrast, there is a totally different type of bladder abnormality in males with a history of persistent primary enuresis and also in a few of the proximally obstructed males. Here the bladder is of normal speed but is abnormally strong, suggesting that true hypertrophy has occurred. The reasons for and clinical significance of these differences in bladder function remain to be found out.

Females

In the females the typical abnormalities of bladder function seem to be the opposite of those in the males, but the differences between clinical categories are less obvious. There is no convincing mechanical evidence of detrusor hypertrophy in any group. Even in category (v), the primary enuretics, although some bladders have values of P_{iso} at the upper limit of the normal range, others have low values of P_{iso}. There is no evidence of a group with slow bladders and obstructed urethras. (Urethral obstruction is rare in females.) Most non-normal females complain of stress or urge incontinence or of urgency, and many of them seem to have weak, low-pressure bladders (sometimes unstable), just as at rest, they have low-pressure urethras (Griffiths, 1973). So in these females the whole lower urinary tract seems to work at low pressure.

Summary

Bladder function in micturition may be studied, without interference from the urethra, through 2 parameters, P_{iso} and Q^*, which are measures respectively of the maximum pressure and of the maximum flow rate that the bladder can generate, *i.e.* of its intrinsic strength and speed. These parameters may be determined in a standard urodynamic investigation if the patient interrupts voiding for a short time with the external sphincter.

The normal ranges of P_{iso} and Q^* depend only slightly on age and sex and seem to be as follows: P_{iso}, 50 to 100(+) cm H_2O in both sexes; Q^*, 35 to 120 ml s^{-1} in males, 20 to 80 ml s^{-1} in females. There are significant differences in both parameters between different groups of patients. Many females, with stress or urge incontinence or with urgency, have bladders which seem to be weaker than normal (low P_{iso}). The majority of proximally obstructed males, and many who have been surgically relieved of obstruction, have bladders which are significantly slower than normal but are of normal strength (low Q^*, normal P_{iso}). Therefore the characteristic response of the detrusor to obstruction appears to be not the expected mechanical hypertrophy (Turner Warwick *et al.*, 1973) but reduction in intrinsic speed. In contrast, a few proximally obstructed males and most males with a history of primary enuresis (persisting after 6 years of age) have bladders of normal speed and of strength significantly greater than normal (normal Q^*, high P_{iso}), suggesting true mechanical hypertrophy of the detrusor. Females with a history of primary enuresis do not show this pattern so clearly.

Since these sex- and disease-related differences must surely be of clinical significance, and since it is so easy to measure P_{iso} and Q^* by the method given in section (e) of the Appendix, those who are concerned with clinical urodynamics are urged to investigate bladder function in this or some equivalent way (*e.g.* that proposed by Schäfer and Melchior (1975)).

Appendix: Calculation of the Parameter Q^*

(*a*) The BOR is believed to be a reflection of the Hill equation which describes the mechanical behaviour of contracting muscle (Hill, 1938; Griffiths, 1973). It follows with certain assumptions that Q_m should be proportional to $V^{1/3}$, where V is the volume in the bladder (Drolet and Kunov, 1975; Schäfer and Melchior, 1975), rather than to $V^{1/2}$ as we have assumed on the basis of previous clinical measurements. In fact proportionality to $V^{1/2}$ and proportionality to $V^{1/3}$ would not be distinguishable either in the previous measurements or here.

(*b*) Because the exact form of the BOR is not known, the estimate Q^* is obtained in the simplest possible way, that is by *linear* extrapolation (see Fig. 2). Q^* is clearly smaller than the true value of Q_m for the standard bladder volume. The standard Hill equation (which is correct for striated muscle but not necessarily for the smooth muscle of the bladder) suggests that Q^* should vary from $Q_m/5$ when $\Delta P/P_{iso} \to 0$ to $Q_m/3$ when $\Delta P/P_{iso} = \frac{1}{2}$, where ΔP is the rise in detrusor pressure when voiding is interrupted. Even if this variation were allowed for, inspection of the data shows that it would make no significant difference to the conclusions.

(*c*) Part of the detrusor pressure is due not to active muscular contraction but to passive elasticity of the bladder wall. Both contributions are included in the values of P_{iso}. However, the passive contribution is not governed by the Hill equation and should not be included when Q^* is calculated. The passive contribution may be roughly estimated from the detrusor pressure measured during cystometric filling (provided that there is no active contraction). In practice it makes little difference to the conclusions whether the passive contribution is included or not.

(*d*) For this paper Q^* has been calculated as follows (see Fig. 3). The estimate of Q_m at bladder volume V is

$$Q_m = Q\,(P_{iso}-P_{pass})/\Delta P,$$

where Q is the flow rate just before voiding is interrupted and P_{pass} is the passive detrusor pressure during cystometric filling at the same bladder volume (estimated, if the detrusor contracted actively during filling). Q^* is obtained by correcting to the standard volume of 200 ml:

$$\begin{aligned} Q^* &= Q_m\,(200/V)^{\frac{1}{2}} \\ &\doteq 14Q\,(P_{iso}-P_{pass})/(\Delta P\; V^{\frac{1}{2}}). \end{aligned}$$

Occasionally the patient did not succeed in entirely stopping the flow: this too has been allowed for. It is possible in practice to calculate Q^* from the drop in pressure that occurs when flow starts again after the interruption, but this is more difficult because an ordinary flowmeter cannot measure the flow rate Q immediately after restarting.

(*e*) Q^* may usually be calculated with sufficient accuracy by the following rule-of-thumb procedure. (i) Ensure that, when the patient interrupts voiding by use of the external sphincter, the volume in the bladder is between 100 and 400 ml. This makes correction to the standard volume (200 ml) unnecessary. (ii) Note the flow rate Q immediately before the interruption, and the rise ΔP in detrusor pressure and the isometric detrusor pressure P_{iso} just after interruption (see Fig. 3). (iii) Calculate $Q\,(P_{iso}/\Delta P)$. This is approximately equal to Q^*.

I am grateful to Dr C. G. Whiteside and other members of the clinical urodynamic unit of the Middlesex Hospital, London, for allowing me to make use of their records and for their hospitality. I am indebted to them and to Dr W. Schafer of the Department of Urology, Aachen Technical University, for many helpful discussions.

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The Author

D. J. Griffiths, PhD, Lecturer in Physics.

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Recurrent Stress Urinary Incontinence in the Female

J. EDWIN MORGAN and GRANT ANGUS FARROW

Department of Obstetrics and Gynaecology, and Department of Surgery, University of Toronto, and Toronto General Hospital

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Although incontinence is an uncommon problem in the male, it is one of the commonest urological complaints in the female. For the urologist recurrent stress incontinence is more common than primary stress incontinence. In those patients who have had one or more previous vaginal or suprapubic operations a repair is best accomplished by a 2-team abdominal-vaginal approach using a wide band of inert polypropylene mesh (Marlex)[1] (Fig. 1). The safety and success of the procedure depends on the wide mobilisation of the bladder and urethra with release from dense pelvic scar followed by suspension of the bladder neck in a high retropubic position.

Patients

From 1st January, 1968 to 31st December, 1975, 1,500 females presenting with recurrent urinary incontinence were reviewed by one of us (J. E. M.) at the Urological-Gynaecology Clinic at the Toronto General Hospital. 25% eventually required surgical correction and 8% of the total (127 patients) were treated with the 2-team Marlex sling repair. This group had an average of 2·4 previous unsuccessful procedures for incontinence, not including hysterectomy.

Methods

The precise technique of the operation has been previously described (Morgan, 1970). The complete mobilisation of the urethrovesical junction suprapubically and vaginally prior to placement of the sling is best accomplished by a 2-team, abdominal-vaginal approach with a gynaecologist below and a urologist above. Marlex mesh is attached to Cooper's ligaments and this provides a broad flat hammock supporting the bladder neck in a high retropubic position (Fig. 2).

Results

118 patients had no further anatomical stress urinary incontinence. 9 patients were classed as failures because of persistent symptoms. 4 of these patients have a significant degree of urgency incontinence associated with persistent urinary infection. 3 are incontinent due to a failure of technique with improperly placed slings. 1 patient developed multiple sclerosis and 1 hysterical patient continued to complain of incontinence even after an ileal conduit diversion.

Complications have been infrequent. 4 patients had persistent poor bladder emptying, all were cured with an anterior transurethral resection of bladder neck. 1 of these patients had a urethral

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[1] Marlex is manufactured by Usher's Marlex Mesh, Davol Rubber Company, Providence, Rhode Island.

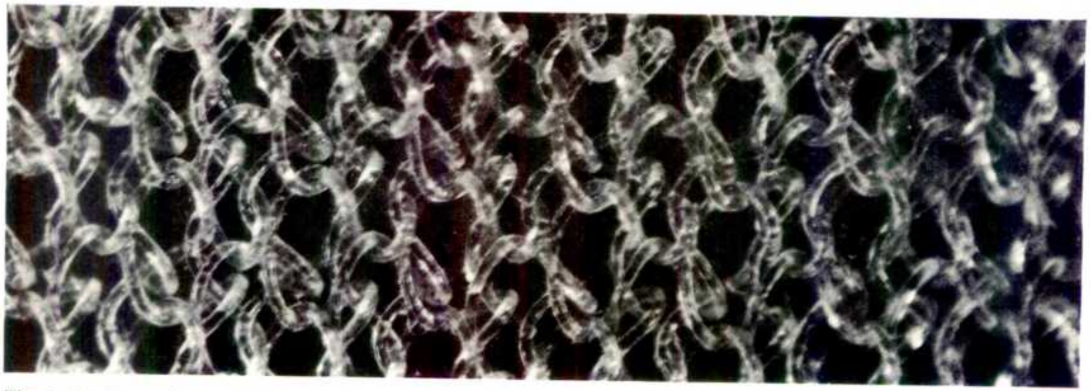

Fig. 1. Marlex mesh.

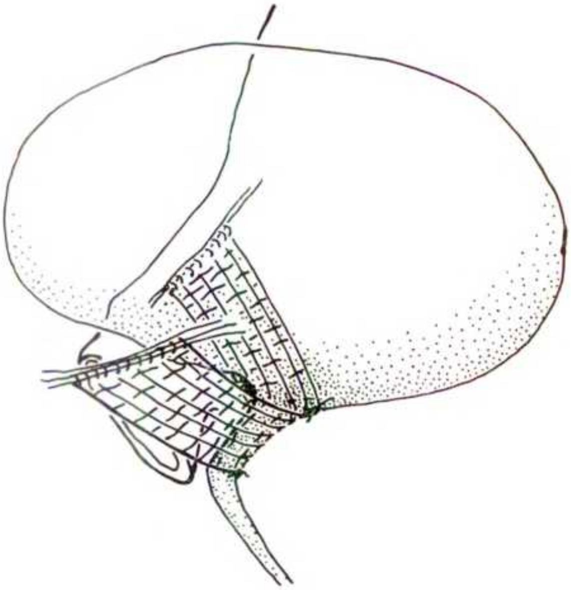

Fig. 2. Marlex sling.

stone. 2 patients with prolonged cystitis are now free of infection and off medication. 3 patients had a postoperative wound infection. There were no significant cardiopulmonary or thromboembolic phenomena, no fistulae, and no slings have had to be removed.

Discussion

A complete history with pelvic examination, cough test, and urinalysis is usually done by all examiners; however, to complete the investigation a cystoscopy and cysto-urethrogram should always be performed. Stress incontinence and urgency incontinence are frequently seen in combination. For this reason each patient must be cystoscoped, a procedure seldom carried out by the gynaecologist. The patient with urethral, bladder neck or trigonal irritation will be improperly diagnosed and perhaps subjected to unnecessary surgery. One must also assess the degree of

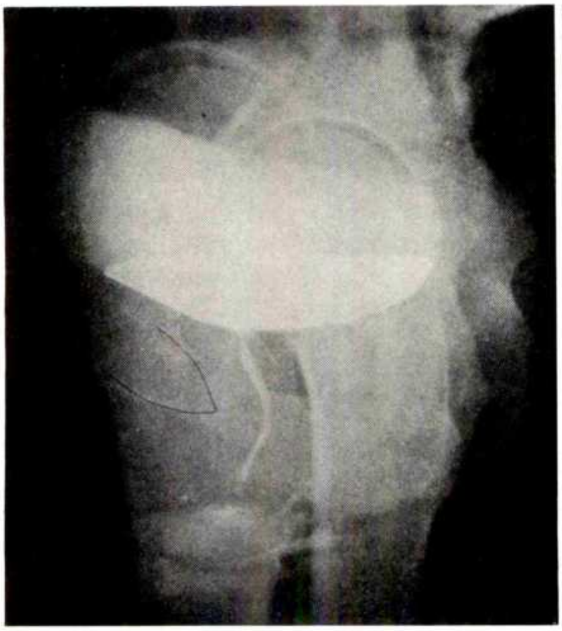

Fig. 3. Normal cysto-urethrogram.

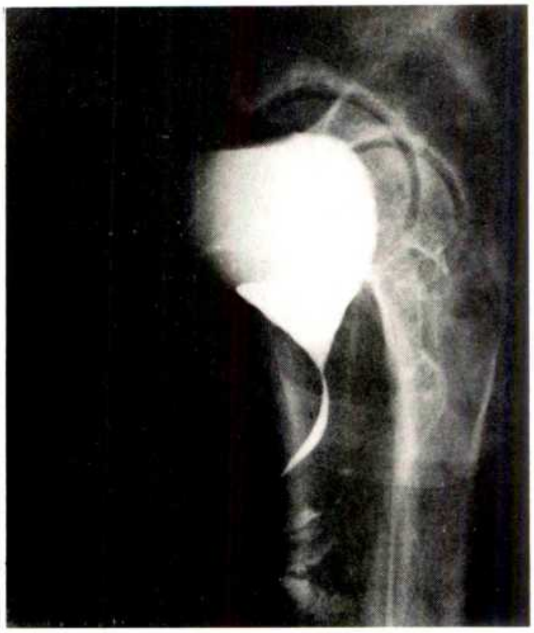

Fig. 4. Dependent urethrovesical junction.

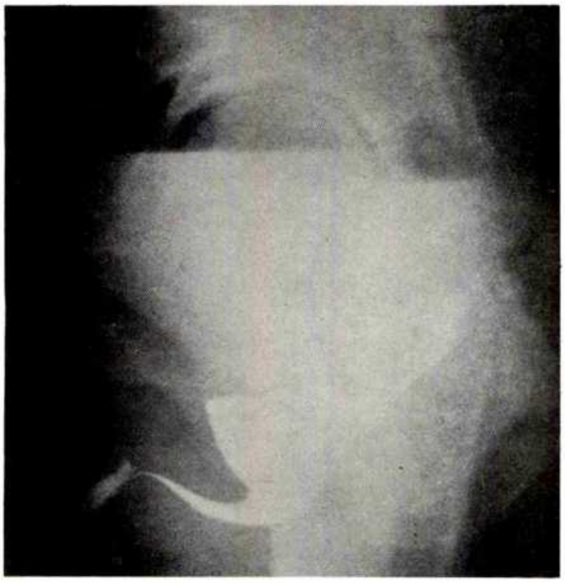

Fig. 5. Incompetent urethrovesical junction with vaginal prolapse.

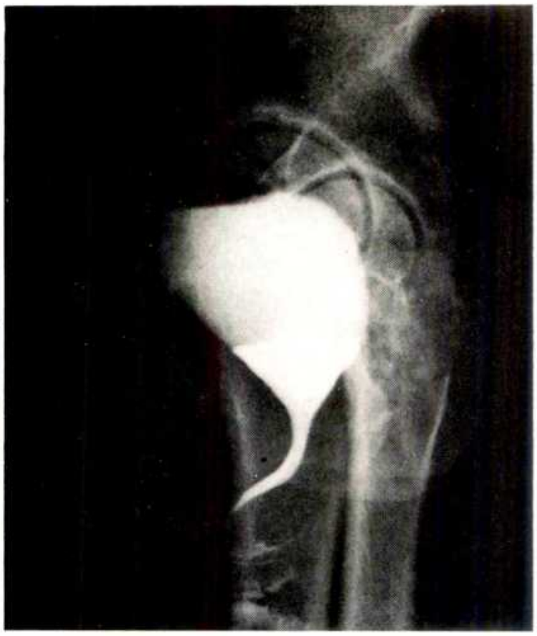

Fig. 6. "Drain pipe" urethra.

incontinence. 50% of normal nulliparous females have some degree of urine loss with a sudden coughing or laughing and this must be considered within the range of physiologic normal.

Traditionally, the patient with incontinence is seen and treated by the gynaecologist with a vaginal repair. If this procedure fails the patient is referred to the urologist who then performs a suprapubic Marshall Marchetti operation. In assessing long-term (5 years) results of treatment of stress incontinence the generally accepted figures reveal: the vaginal approach yields slightly above 50% cure rate, while the suprapubic approach yields slightly above 80% cure rate. With such a difference, why is the vaginal approach still used so frequently? If one assesses the woman presenting with stress incontinence vaginal prolapse syndrome, one-third present with pure stress incontinence with little or no prolapse, one-third present with simple vaginal prolapse without incontinence, and one-third present with a combination of both. It is clear that two-thirds of patients initially present with some degree of vaginal prolapse. Associated factors in this presentation that must be considered are multiparity with stretching of tissues, the older patient with loss of oestrogen and thinning of tissues, chronic chest disease, strenuous activity, and obesity.

If the gynaecologist is lax in having cystoscopies performed on these patients, the urologist is frequently as lax in not radiologically demonstrating the defect. The key to treatment is the precise demonstration of the anatomical defect in the urethra. The anatomy of the base of the bladder and urethra is best seen on the lateral view of a barium paste, hypaque static cysto-urethrogram (Low, 1967). Fig. 3 shows a tracing of the normal cysto-urethrogram demonstrating a high retropubic position, the urethrovesical junction is not dependent, and the urethra has a normal S-shaped curve with the upper third of urethra closed. With straining there is a slight normal descent, slight posterior rotation and the upper third of the urethra remains closed. It becomes obvious that this must not be a voiding study, *i.e.* we want to see this junction in resting and stress conditions while not voiding. During voiding the junction normally opens and becomes incompetent. If this junction (and the term "junction" rather than "angle" is stressed) is the dependent

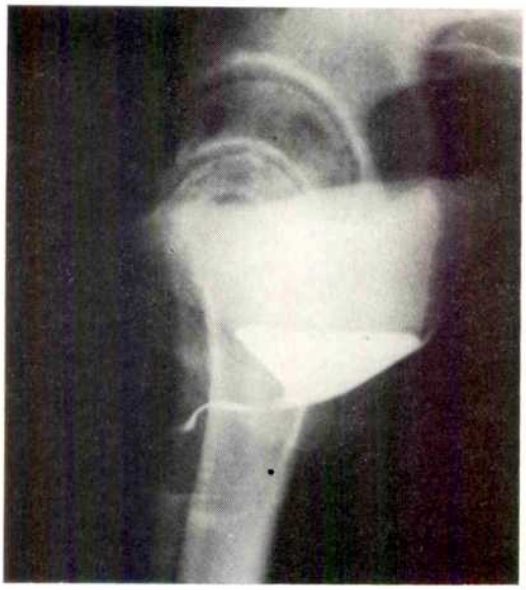

Fig. 7. Anterior funnel.

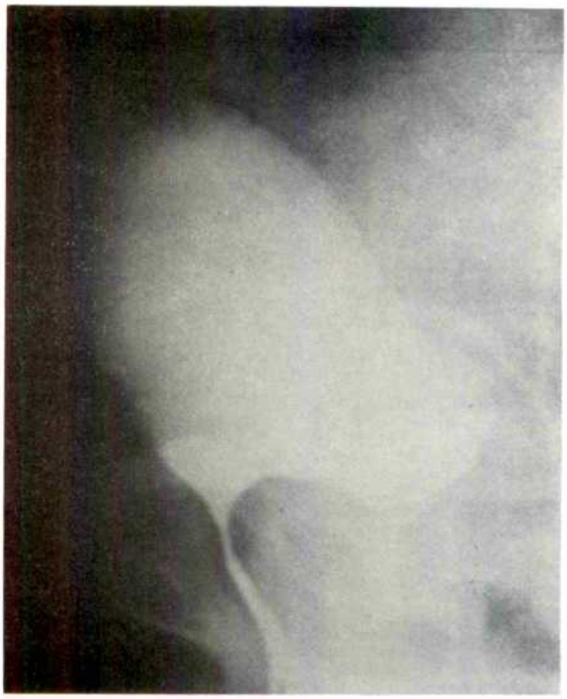

Fig. 8. Cysto-urethrogram following Marlex sling.

portion of the bladder at the base of a funnel, with abdominal pressure directed here, the patient will probably have stress incontinence. This is demonstrated in Figure 4. Another advantage of this X-ray is the ability to document what has been accomplished postoperatively.

As noted previously, two-thirds of these patients present with some degree of prolapse and some of these quite correctly should be treated by a vaginal repair. This is particularly so if there is significant descent which can be elevated by vaginal sutures. This is shown in Figure 5 in a patient presenting with severe stress incontinence. Her X-ray shows the urethrovesical junction and upper third of the urethra to be grossly incompetent and dependent, presenting in the perineum. Clinically, she had marked ureterovaginal prolapse. This patient was treated and cured with a vaginal repair. The reason, however, that there are generally such poor results with vaginal repair is that one is able to elevate the junction just so far, and in 50% of cases this is not far enough.

The Marshall test is not particularly reliable in this regard. Vaginal sutures are frequently not as effective as the finger or forceps in the vagina. The second danger of the vaginal repair occurs in patients with vaginal prolapse and minimal stress incontinence. Repair of the cystocoele may produce severe incontinence by placing the urethrovesical junction at the most dependent portion of the bladder.

The suprapubic approach, on the other hand, yields a success rate of over 80%. One can elevate the junction much higher and it is therefore the procedure of choice in patients with stress incontinence with little retropubic descent and without symptomatic vaginal prolapse. A factor worth noting in the primary suprapubic operation is that by lifting the anterior wall of the vagina, one may make a mild enterocoele progressively symptomatic requiring a subsequent vaginal repair. Although the Marshall-Marchetti procedure is the most frequently employed suprapubic operation, the Burch sling (Burch, 1961; Morgan, 1973) employing the vagina as a hammock to Cooper's ligaments is a very effective procedure in cases not having had previous vaginal surgery.

For the urologist the problem of recurrent stress incontinence is more common than primary stress incontinence. In this situation one must be careful to rule out other underlying causes of incontinence. Occasionally, one will find a previously unrecognised neuropathic element or underlying urinary infection. The success rate of treatment is poorer in all procedures following one or more previous vaginal or suprapubic operations. The poor results in the treatment of recurrent stress incontinence are primarily for one reason only—pelvic scar. Figure 6 shows a fixed, "drain-pipe" urethra in the dependent position of the bladder in a patient who had 2 previous vaginal operations and 2 previous suprapubic operations.

The suprapubic procedure alone does not release the posterior aspect of the urethra in the dense scar of the vagina following repeated colporrhaphy. As shown in Figure 7, a Marshall procedure in this situation has further opened the urethra creating an anterior funnel, aggravating the stress incontinence. This patient has had 2 vaginal repairs and 1 previous Marshall Marchetti procedure.

It is therefore important that the procedure chosen to correct the defect in patients with recurrent stress incontinence after one or more vaginal and/or suprapubic operations must: 1, release the anterior scar in the space of Retzius; 2, release posterior scar in the vagina; 3, adequately elevate the junction so it is not the dependent position at the base of the funnel.

This is effectively accomplished by the 2-team Marlex sling as seen in Figure 8.

Summary

1,500 females presenting with recurrent urinary incontinence were investigated in depth. 27% required further surgery, 127 of whom were treated with a 2-team Marlex sling.

Careful assessment is the key to treatment including cystoscopy and good radiological documentation.

One must be aware of the capabilities and limitations of the various procedures employed for stress incontinence and select the correct procedure for the given problem.

When dealing with recurrent stress incontinence the surgical procedure must take down all periurethral scar, anteriorly and posteriorly and adequately elevate the urethrovesical junction so it is not the dependent point at the base of the funnel.

The Marlex sling procedure fulfills the above criteria, has been singularly effective, and remarkably free of complications.

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The Authors

J. Edwin Morgan, MD, FRCS(C), FACOG, Associate Professor, Department of Obstetrics and Gynaecology.
Grant Angus Farrow, MD, FRCS(C), FACS, Assistant Professor, Department of Surgery.

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A Preliminary Assessment of Bladder Distension in the Treatment of Enuretic Children

J. M. S. JOHNSTONE, G. M. ARDRAN and P. D. RAMSDEN
Radcliffe Infirmary and Nuffield Institute for Medical Research, Oxford

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Enuresis is correctly regarded as a symptom but in most children no underlying organic disease of psychological disturbance can be demonstrated. In most children the condition will resolve spontaneousely. In others various theraputic measures such as the use of a bell alarm system and tricyclic drugs will be effective. However, there remains a resistant group of children who are persistently enuretic and the social inconvenience to these children and their families is considerable. It is towards the latter group of childaen that this study is directed.

The possibility that prolonged bladder distension might influence enuretic behaviour in children was suggested by a recent publication by Dunn, Smith and Adran (1974), who were successful in relieving urgency, urge incontinence and enuresis in adults, demonstrated to have an unstable bladder.

The object of the present study has been to select a group of resistant enuretic children to exclude gross organic disease and psychological disturbance, to identify those with bladder instability by urodynamic studies and to determine whether or not prolonged bladder distention would influence the course of their enuresis.

Materials and Methods

Patients

22 enuretic children with no evidence of organic disease or gross psychological disturbance and in whom previous treatment with a bell alarm and with tricyclic drugs had been unsuccessful, were selected for urodynamic studies.

The families were interviewed, the children were fully examined and the following investigations performed: a full blood count, serum electrolyte and blood urea estimation, microscopical examination and chemical analysis of urine, culture of urine, intravenous pyelography and micturating cysto-urethrography.

Included in the 22 children were 5 girls who had been treated for urinary tract infections in the past, in 2 the infection being associated with vesico-ureteric reflux. In each girl the most recent micturating cystogram was normal and the urine sterile.

10 of the 18 children had a family history of enuresis affecting at least 1 close relative, sibling, parent, uncle or aunt. A significant social problem was present in families of 7 children, for example, marital disharmony, father unemployed or in jail, mother depressed.

Urodynamic Studies

Both urine flow rates and cystometrograms were recorded in children without the use of anaesthesia or sedation. Preoperative recordings were obtained in all children and postoperative recordings in 9 children.

Table I

Pre and Postoperative Cystometrogram Results and Final Bladder Capacities after Distension. Expected Bladder Capacities taken from Muellner and Starfield

				Cystometry				
				Preoperative		Postoperative		
Child	Age	Sex	Expected bladder capacity	Bladder capacity	Detrusor activity	Bladder capacity	Detrusor activity	Bladder capacity after distension
CB	16	F	500	550	Abnormal	320	Abnormal	725
JB	14	F	450	600	Abnormal	460	Abnormal	525
GM	12	F	400	Small 250	Abnormal	–	–	–
HM	10	F	350	Small 100	Abnormal	Small 90	Abnormal	340
AM	9	F	325	Small 100	Abnormal	Small 100	Abnormal	470
DH	7	F	275	330	Abnormal	300	Abnormal	520
JH	7	F	275	210	Abnormal	–	–	320
PB	6	F	225	Small 100	Abnormal	Small 100	Normal	–
ST	16	M	500	Small 95	Abnormal	–	–	530
AT	13	M	450	Small 200	Abnormal	–	–	480
SP	12	M	400	Small 180	Abnormal	–	–	470
PC	11	M	375	Small 250	Abnormal	–	–	275
SG	9	M	325	Small 95	Abnormal	Small 120	Abnormal	250
MH	9	M	325	Small 175	Abnormal	–	–	–
SW	7	M	275	Small 70	Abnormal	Small 100	Abnormal	210
AD	6	M	225	190	Abnormal	190	Abnormal	475

To obtain a cystometrogram, the child was placed supine and a soft double-lumen Portex catheter passed transurethrally into the bladder to allow simultaneous infusion of saline and recording of intravesical pressure. A second balloon-tipped Portex catheter was passed into the rectum to record intra-abdominal pressure. Where possible two cystometrograms were recorded, the first with an infusion rate of 100 ml/min and the second at 20 ml/min. The child was asked to withhold from micturition as long as possible, to indicate any desire to void and to cough and strain at appropriate intervals. Bladder instability, either spontaneous or induced by straining and coughing, was considered present when the detrusor pressure rose above 15 cm H_2O during the filling phase of cystometry and this abnormality was used as an indication for bladder distension. A further record was made of bladder capacity; a bladder with a volume of less than two-thirds the expected capacity for a child of similar age was considered small; normal values were taken from results given by Muellner (1960) and Starfield (1967).

Cystoscopy and Bladder Distension

Children were admitted to hospital for cystoscopy and bladder distension and the procedures were carried out under general anaesthetic.

After cystoscopy, a balloon catheter was passed transurethrally into the bladder. The balloon was filled with saline from an overhead reservoir and the height adjusted so as to distend the

Table II

Tabulation of the Incidence and Severity of Day Symptoms and Night Symptoms Before and After Bladder Distension, the Parents' Opinion and the Interval Between Distension and Final Assessment

			Day symptoms		Nocturnal enuresis			
Child	Age	Sex	Pre-operative	Post-operative	Pre-operative	Post-operative	Parents' opinion	Period of follow-up
CB	16	F	E 3 U++	E 0 U+	5	2	Improved	1 year
JB	14	F	Nil	Nil	2	0	Symptom free	1 year
GM	12	F	E 2 U ++	E 0 U +	2	1	Improved	1 year
HM	10	F	U ++ F ++	U + F 0	2	7	Improved	1 year
AM	9	F	E 3 U ++	E 3 U ++	7	7	No change	1 year
DH	7	F	E 3 U ++ F +	E 0 U + F 0	7	4	Improved	1 year
JH	7	F	U + F +	U 0 F 0	7	0	Symptom free	1 year
PB	6	F	E 4 U ++ F ++	E 2 U + F 0	7	5	Improved	1 year
ST	16	M	F +	F +	5	5	No change	1 year
AT	13	M	Nil	Nil	3	0	Symptom free	1 year
SP	12	M	U +	U +	7	7	No change	1 year
PC	11	M	U + F +	U + F +	7	7	No change	6 months
SG	9	M	U +	U +	7	7	No change	1 year
SW	7	M	E 4 U ++ F ++	E 0 U + F 0	7	2	Improved	6 months
MH	9	M	U ++ F ++	U 0 F +	7	0	Symptom free	3 months
AD	6	M	E 4 U +	E 4 U +	7	7	No change	1 year

Frequency (F); less than 1 hour, + +; 1-3 hours, +; over 3 hours, 0.
Urgency (U); must immediately void, + +; runs to lavatory, +; goes casually to lavatory, 0.
Diurnal enuresis (E) and nocturnal enuresis are expressed as the number of days and nights wet per week.

bladder to systolic blood pressure. Distension was continued for 2 hours and the capacity of the bladder at the end of the procedure recorded. This closed method of distension was chosen to prevent vesico-ureteric reflux. After the procedure the children were prescribed a 4-day course of Septrin and were discharged home the following day.

Assessment of Results

To allow an objective assessment of the response to bladder distension, the incidence and severity of diurnal and nocturnal enuresis and daytime frequency and urgency were graded and compared before and after treatment. The impression of the parents was also recorded. Follow-up was

Table III

(A)

Results of Bladder Distension on Enuresis in 16 Boys and Girls

	Cured	Improved	No change	Total
Boys	2	1	5	8
Girls	2	5	1	8
Total	4	6	6	16

(B)

Results of Bladder Distension on Enuresis in Children with Nocturnal Enuresis Alone and in Those with Diurnal and Nocturnal Enuresis

	Cured	Improved	No change	Total
Nocturnal enuresis	4	1	4	9
Diurnal and nocturnal enuresis	0	5	2	7
Total	4	6	6	16

arranged at 1 month, 6 months and 1 year after distension. At each follow-up the symptoms were recorded, the child examined, and the urine cultured.

Results

Urodynamic Studies

The urine flow rate in 13 children was within normal limits. The remaining 3 children had voided shortly before the investigation and were unable to pass sufficient urine to give a meaningful result.

Preoperative cystometrograms in 16 of 22 children, 8 girls and 8 boys, were abnormal (Table I). In 11 children the bladder capacity was small and the detrusor activity abnormal, and in 5 children the capacity was normal but detrusor activity abnormal.

Postoperative cystometrograms recorded 1 month after bladder distension in 8 children showed virtually no change from the preoperative recordings. In 2 girls the bladder capacity was slightly reduced, although in 1 of these the degree of detrusor instability was improved.

Cystoscopy

The findings at cystoscopy in 15 children were normal, in 1 girl the bladder wall was slightly trabeculated, but in this case there was no evidence of outlet obstruction.

Results of Distension

The final assessment of symptoms was made 1 year after distension in 13 children, at 6 months in 2 children and at 3 months in 1 child (Table II). Of the 16 children, 4 were symptom free, 6 were improved and 6 unchanged.

7 of 8 girls benefited to some extent from bladder distension, as compared with only 3 of 8 boys. 5 of 7 children with nocturnal and diurnal enuresis benefited as compared with 5 of 9 children with only nocturnal enuresis (Table III).

Of 10 children with frequency during the day, 6 developed a normal voiding pattern and 2 were improved. Of 12 children with urgency during the day, 2 were symptom free, 5 improved and 5 unchanged.

Discussion

Routine use of extensive investigation of enuretic children is neither necessary nor desirable. In this study, however, urodynamic studies were essential to provide a scientific basis for selection of children for bladder distension and for the assessment of results.

Cystometry

Cystometry is a difficult procedure in children and the results should be interpreted with caution. Passing a urethral catheter causes distress and considerable patience is then needed to encourage the child to relax and co-operate during the filling phase of the recording. The use of a rectal pressure line is essential both to record changes in intravesical pressure that are due to detrusor activity as opposed to changes in intra-abdominal pressure, and to indicate that the child is fully relaxed. It must also be remembered that normality of a cystometrogram in the child is judged against what is considered normal or abnormal in an adult; there are no control series available in children.

80% of children in this series (16 of 22) showed evidence of bladder instability, a similar finding to that of Pompeius (1971), who demonstrated abnormal detrusor function in 80% (48 of 63) of enuretic children, and to Arnold (1974) who found bladder instability in 90% of patients with persistent enuresis. In this study, bladder instability was found in children with both nocturnal and diurnal enuresis and in those with nocturnal enuresis only. This finding is unlike that reported by Whiteside and Arnold (1975) who found that patients with diurnal and nocturnal enuresis had mainly abnormal detrusor function and those with nocturnal enuresis alone had mainly normal detrusor function.

Zaleski, Gerrard and Shokeir (1973) found that the maximum and the mean bladder capacity in enuretic children was less than in their peers. In this study, bladder capacity measured at cystometry was small in 12 of 22 children; the boys were predominant in this group, 8 of 11 having a small bladder as compared with 4 of 11 girls. Furthermore, the bladder capacity in 5 children, 3 boys and 2 girls, after 2 hours' distension remained less than the mean functional bladder capacity of a normal child of the same age.

Response to Distension

The results of treatment for enuresis are notoriously difficult to assess. It must be remembered that in any group of enuretic children, 10% will resolve spontaneously in 1 year. Furthermore, admission of an enuretic child to hospital or the prescription of a placebo will often be followed by a short-term remission of symptoms. Longer-term results are required before a new form of treatment can be assessed, and in this series, in 13 of the 16 children, the result of treatment has been analysed after an interval of 1 year.

The results are disappointing when compared with those reported in adults. Dunn *et al.* (1974) found that 10 of 13 patients with nocturnal enuresis were dry after bladder distension, the follow-up period ranging from 3 to 10 months. There are interesting differences between the report by Dunn and the present study. In the former, the patients were adults, they suffered more from day symptoms, cystoscopy showed that most of them had marked trabeculation, epidural as opposed to general anaesthesia was used, and postoperative cystometrograms showed considerable improvement in detrusor function.

Bladder Neck Obstruction

Mahony (1971) reported bladder-neck obstruction and secondary hypertrophy of detrusor in 95% of a group of enuretic boys and 71% of enuretic girls. In this study, micturating cystourethrography, urine flow rates and cystoscopy provided no evidence of bladder-neck obstruction in any child.

Adverse Effects of Distension

There were no immediate or long-term complications from bladder distension. 3 children had troublesome frequency and urgency which lasted less than 7 days after the procedure. Urine cultures taken routinely in all children at follow-up clinic were sterile.

Social and Family History

The incidence of social problems and relatives with a history of enuresis is similar to that in many series of enuretic children. It is interesting, however, to note the co-existence of social problems which must to some extent disturb the child psychologically and evidence of detrusor instability as demonstrated by urodynamic studies.

Summary

Urodynamic studies were performed in 22 enuretic children. Each child had previously been investigated to exclude gross psychological disturbance and organic disease and had been treated unsuccessfully in the past by conventional means.

16 of the 22 children showed evidence of bladder instability and were subjected to bladder distension. At follow-up, 4 children were in complete remission of symptoms, 6 had improved and 6 showed no change; the girls responded better than the boys.

The interpretation of urodynamic studies, the significance of the results of bladder distension and the possible role of detrusor instability in the aetiology of enuresis are discussed.

We would like to thank Mr J. C. Smith for his advice and help in the design of this trial, Miss Fursdon of the Nuffield Institute for assistance with cystometry, and Miss Fergusson for preparing the manuscript.

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The Authors

J. M. S. Johnstone, FRCS, Surgical Tutor, Radcliffe Infirmary. (Now Consultant Surgeon, The Leicester Royal Infirmary, Leicester.)

G. M. Ardran, MD, FRCP, FRCR, Radiologist, Nuffield Institute for Medical Research, University of Oxford. Consultant Radiologist, United Oxford Hospitals.

P. D. Ramsden, FRCS, Research Registrar.

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Short Case Report

Acute Retention of Urine in a Woman due to an Exoenteric Leiomyoma

Case Report

A 40-year-old woman presented with a 15-hour history of increasing lower abdominal pain and difficulty in passing urine which led to complete retention. She had no previous urinary symptoms and was not shocked. A urethral catheter drained 1,100 cc of sterile urine containing a trace of protein and a few red blood cells. Initial cystoscopy and examination under anaesthetic showed a tight urethra, normal bladder and a large cystic lesion in the left lower abdomen, thought to be an ovarian cyst.

She was transferred to the gynaecology department of the district hospital where the diagnosis of a ruptured ovarian cyst was made. At laparotomy, a large cystic tumour was found to have ruptured leading to a haemoperitoneum. It was attached to the mesentery close to the small bowel, 70 cm from the ileocaecal valve, by a stalk containing lymph nodes. Removal of the tumour necessitated resection of 7 cm of bowel.

24 hours postoperatively, she had to be re-catheterised, after which recovery was uneventful.

The tumour was histologically a benign exoenteric leiomyoma arising from blood vessel muscle, or muscle fasciculi in the peritoneum and attached to the normal ileum by a non-muscular tissue stalk.

Comment

Retention may have been due to increasing neuromuscular dysfunction caused by pain making voiding impossible, or an extrinsic pressure effect of a pelvic tumour on the bladder neck resulting in compression and elongation of the urethra (Ward *et al.*, 1968).

We believe this is the first report of this tumour causing acute retention of urine in a woman.

J. E. Carvell* and S. M. Stubbs
Departments of Surgery, Obstetrics and Gynaecology, Southampton General Hospital

* To whom requests for reprints should be made.

We should like to thank Mr J. D. Jenkins for permission to publish details of this case.

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Massive Bladder Stone

J. P. WILLIAMS, M. E. MAYO and N. W. HARRISON
St Peter's Hospital, London

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Very large bladder calculi were rare even in the 17th to 19th centuries when bladder stones in general were common. It was an unexpected reminder of the past when three such cases were recently treated at St Peter's Hospital for Stone.

Case 1

A 56-year-old salesman presented with a 2-week history of difficulty in micturition and interruption of the stream. There had been no frequency and no haematuria during this period, but some 2 years before, the patient had a brief episode of similar symptoms when blood was noticed in the urine. His past medical history was otherwise

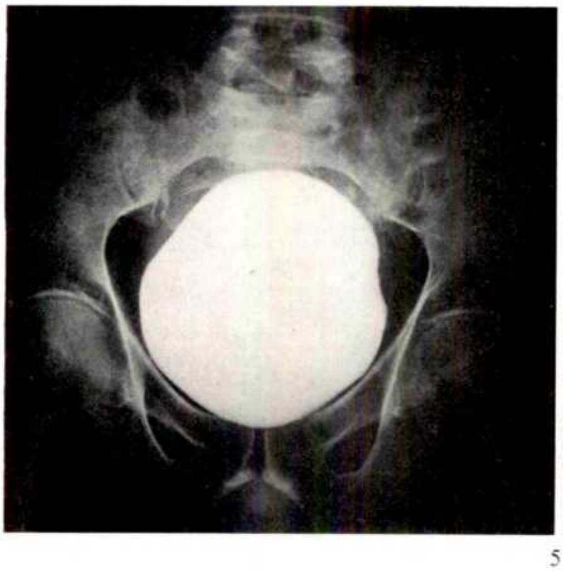


Fig. 1. Case no. 1. Plain X-ray.

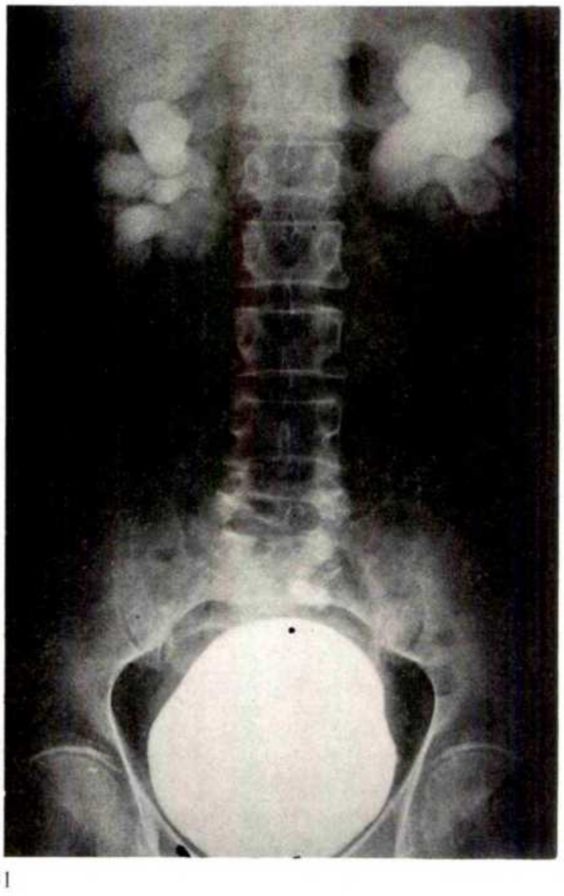


Fig. 2. Case no. 1. IVU showing bilateral hydronephrosis and hydroureter.

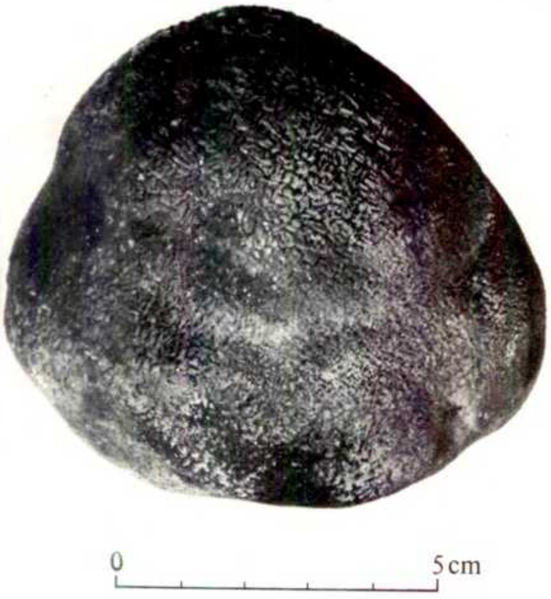


Fig. 3. Case no. 1. The stone weighing 1·13 kg. The circumferential groove due to the pelvic brim is clearly seen.

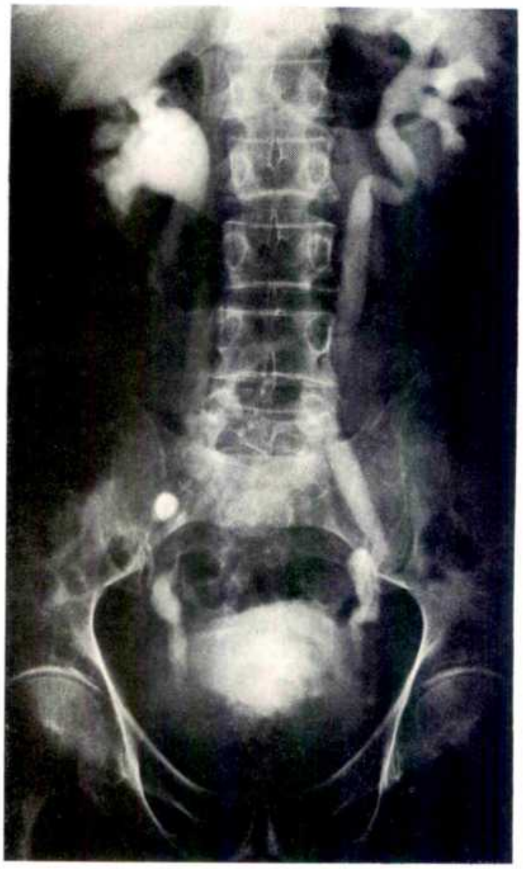


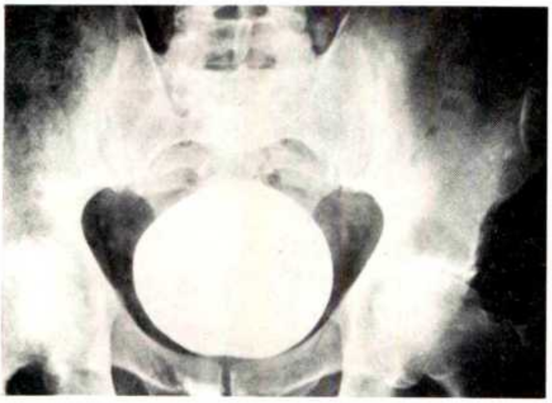
Fig. 4. Case no. 1. IVU 3 months after removal of bladder stone.

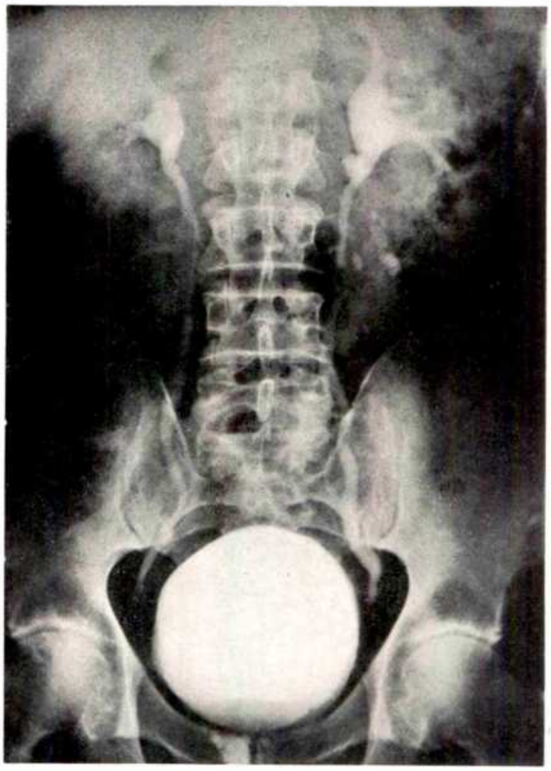
without incident and there was no family history of urological disease. General physical examination was unremarkable but on rectal examination a very firm area of induration at the bladder base was noted and was thought to suggest a neoplasm. The prostate was not enlarged. The urine was sterile on culture and contained a few white cells. The haemoglobin, blood urea and serum creatinine were normal. Plain X-ray of the abdomen (Fig. 1) revealed a massive bladder stone and urography (Fig. 2) showed bilateral hydroureter and hydronephrosis. The patient was admitted to St Peter's Hospital, where metabolic screening gave no evidence of abnormal calcium metabolism. At operation one regretted having spurned the registrar's offer to obtain a pair of obstetric forceps: the stone was systolically embraced by the bladder and having completely filled the bony pelvis had continued to grow up into the false pelvis so that it was impacted under the pelvic brim. When the fundus of the bladder was incised no urine escaped. Eventually, after a period of teasing of the stone by the surgeon and of the surgeon by the registrar, the stone was delivered. There being no prostatic enlargement an anterior YV-plasty of the bladder neck was carried out and the bladder closed in two layers with urethral catheter drainage. Recovery was uneventful. On examination the stone weighed 1·13 kg and measured 10·4 cm across its maximum diameter. Its inferior aspect bears a smooth heart-shaped impression of the trigone and towards its upper part may be seen a circumferential groove formed by the pelvic brim as the stone continued to enlarge upwards through it (Fig. 3). Analysis of a drill specimen from the stone showed it to consist of calcium 27·2 %, phosphorus 17·3 %, magnesium 0·2 % and oxalate 1·8 %. An intravenous pyelogram carried out 3 months later (Fig. 4) showed that the obstructive changes of the upper tracts were resolving.

Case 2

A 66-year-old chauffeur was referred to St Peter's Hospital with a 10-day history of backache. His general practitioner had found a hard prostate and the patient admitted to symptoms of mild prostatism for some years. There was no relevant past medical history and in particular the patient denied any pain on micturition or haematuria. Physical

Figs. 5 and 6. Case no 2. Plain X-ray and IVU showing bladder stone and upper urinary tracts.

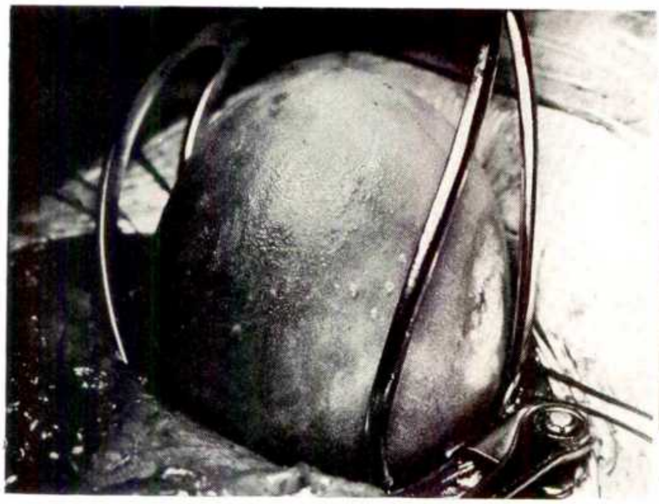




examination was unremarkable, except for his prostate which felt hard, and a clinical diagnosis of carcinoma was made. The urine was sterile on culture and contained only a few white cells. Haemoglobin, urea, creatinine and electrolytes were normal. Plain film and excretion urogram (Figs. 5 and 6) showed a massive bladder calculus, prostatic calculi and mild ureteric stasis. The bladder stone was removed by a transvesical approach and, forewarned by the experience with the previous case, Wrigley's obstetric forceps were employed (Fig. 7). The posterior bladder neck, fibrous prostatic tissue and associated calculi were also removed and no malignancy was found on histological examination. There were white patches on the bladder wall, particularly over the base, and biopsy showed that these were areas of leukoplakia. Following the operation recovery was uneventful. The stone (Fig. 8) weighed 555 g when dry and consisted largely of calcium phosphate with a variable amount of magnesium ammonium phosphate (MAP) and very little calcium oxalate. The largest amount of MAP was found near the surface. Metabolic investigations showed hypercalciuria (462 mg/day). The patient is being reviewed cystoscopically at regular intervals because of the vesical leukoplakia.

Case 3

A 66-year-old retired messenger was admitted with a 2-week history of haematuria. Apart from frequency and dysuria for 2 weeks prior to this he had had no previous urinary symptoms. On physical examination the bladder was palpable and the prostate small; a hard mass felt rectally was thought to be in the colon. The urine contained glucose and was infected with a Gram-positive micrococcus. Fasting blood sugars confirmed diabetes mellitus; urea, creatinine and serum electrolytes were all normal. Radiological examination of the urinary tract showed a very large bladder calculus but normal upper urinary tracts (Figs. 9 and 10). After the diabetes had been controlled the stone was removed by suprapubic lithotomy; ovum forceps were used to facilitate extraction of the stone. No surgery to the bladder neck was performed as the patient denied symptoms of outflow obstruction and had a flow rate of 10 ml per sec in the presence of the stone. Subsequently, however, satisfactory voiding was not established until a transurethral resection of the prostate had been performed. The stone weighed 390 g. Chemical analysis showed it to consist of calcium phosphate and between 26 to 33% magnesium ammonium phosphate (MAP),



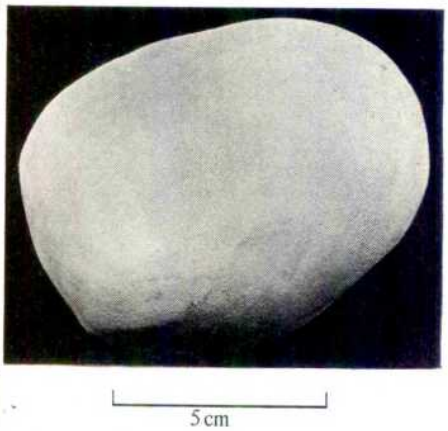


Fig. 7. Case no. 2. Removing the stone with the aid of Wrigley's obstetric forceps.

Fig. 8. Case no. 2. The stone weighing 555 g.

with a trace of calcium oxalate in the surface layer. Biochemical investigations showed no abnormalities of calcium metabolism.

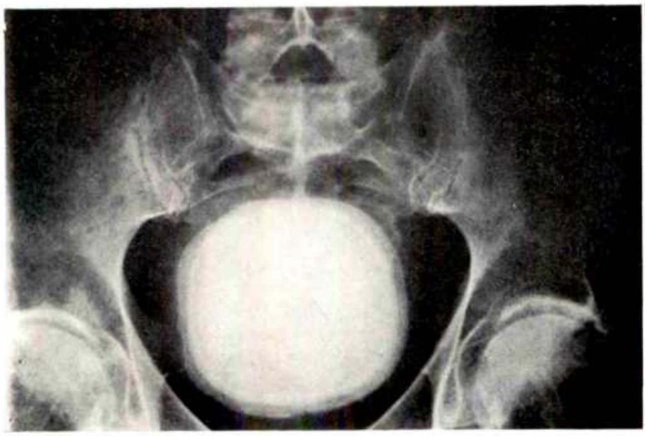
Comment

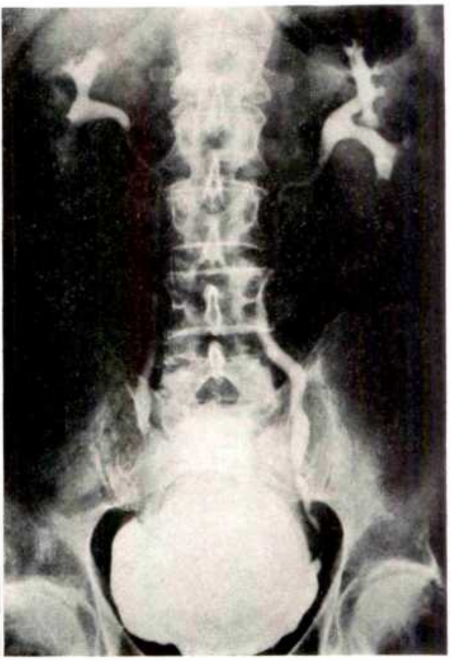
It is astonishing in the first case, where the bladder cavity was replaced by a gigantic stone and the ureters compressed, that any urine found its way into the bladder and out into the urethra. It is difficult to imagine quite how the bladder emptied with such a massive calculus within it, for urine secretion pressure and ureteric peristalsis must have overcome the sheer weight of the stone and urine reached the urethra mostly by bladder neck and external sphincter relaxation, any expulsive component of the detrusor being largely a spent force around the stone. Yet none of the patients had troublesome symptoms. It may be that a large calculus is no more disturbing than a slowly accumulating chronic retention, the symptoms of which many patients ignore until overflow incontinence develops.

The story of bladder stone is amongst the "longest and most intriguing in medical history" (Ellis, 1969) and the reader's attention is drawn to Batty Shaw's fascinating paper on the Norwich School of Lithotomy (1970). In this country, very large bladder stones have been reported from time to time. About the year 1670 a Bury St Edmund's locksmith's wife had one such removed after death. It weighed "33 ounces, 3 drams, 36 grains" (950 g) and measured 11 × 8 cm. Even in that age of florid pathology it was sufficiently notorious for Charles II to ask to see it when he visited those parts. It was in due course presented to the library of Trinity College, Cambridge, where Heberden saw it, and he described it in a paper (Heberden, 1750). This stone could be seen in the Urology Department of Addenbrooke's Hospital until 2 years ago, but has at present disappeared. Those admirable lithotomists, the French, had an even bigger one, however, kept in a chest at La Charité "pesant 51 ounces, qui sont trois livres, trois ounces, quit a est tiree dans cet Hospital au mois de Juin 1690" (1·44 kg), and seen by Dr Lister in 1698: "It was cut from a Monk, who died in the very Operation" (Lister, 1699).

Perhaps the largest stone ever seen in England was that recorded by Sir James Earle in 1809. This weighed 44 ounces troy (1·36 kg) and was 16 inches round its long and 14 inches round its short axis. It could be seen at the Royal College of Surgeons of England until the night of 10th May, 1941. Its story may be read in the College Catalogue of Calculi.

Figs. 9 and 10. Case no. 3. Plain X-ray and IVU showing bladder stone and upper urinary tract.





In an entertaining account of self-performed operations for stone in the bladder Murphy (1969) describes that of the draper of Glasgow which weighed 15½ ounces (440 g) and measured 26·5 cm round its long and 20 cm round its short axis.

Massive stones such as those described here are very seldom seen. Of the Bury St Edmund's stone Heberden wrote, "She had felt much less Pain than might have been expected from so large a stone; and might probably have lived much longer with it, if she had not thought herself to attempt a journey on Horse-back; for while she was riding she was suddenly seized with violent Pains, that obliged her to be taken off the Horse immediately; After which she could never make water, unless the stone was first removed and she continued in great Agonies till she died".

The patients here described had no pain at all.

An explanation of large stones causing little pain may be that stones of this size have no room to move, so that they neither abrade the trigone nor impact in the urethral orifice.

Summary

3 cases of massive bladder calculus are described and are of interest not only because they are rare, but also because of the remarkably few symptoms they produced.

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The Authors

J. P. Williams, MChir, FRCS, Consultant Surgeon.
M. E. Mayo, MS, FRCS, Senior Lecturer (now Assistant Professor, Department of Urology, University of Washington Medical School, Seattle, Washington, USA).
N. W. Harrison, MD, FRCS, Senior Registrar (now Consultant Urological Surgeon, Brighton, Sussex).

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Cystitis Cystica: Characteristics of the Disease in Children

G. VLATKOVIĆ, I. BRADIĆ, V. GABRIĆ and D. BATINIĆ

Department of Paediatric Nephrology and Department of Paediatric Surgery and Urology, University Hospitals Salata and Rebro, Zagreb, Yugoslavia.

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Cystitis cystica is a pathological condition affecting the urinary bladder which is characterised macroscopically by the presence of multiple, small, round raised areas of yellow, brown or pearl colouration on the mucous membrane. Histologically, the lesions are seen to be composed of collections of lymphoid cells. Few reports of the condition affecting children have appeared in the literature; although Kaplan and King (1970) recorded 18 cases none of these were infants. During the last 10 years we have performed cystoscopy in 1823 children with urinary infection or urinary tract anomalies and have found 157 examples of cystitis cystica.

Patients, Investigations and Results

The youngest patient was 9½ months of age and the oldest 14 years; the majority were between 4 and 10 years old. There were 153 girls and 4 boys. All patients had symptoms of urinary infection; in 86 these had been present for 1 year or more and in 114 they had been recurrent. Most children complained of frequent and painful micturition and wetting and often the urine was noted to be cloudy and offensive. Fever, anorexia, abdominal or lumbar pain and vomiting were other common features.

Cystoscopic examination showed, in all cases, inflammatory changes in the mucosa, including hyperaemia and, in some, fibrin deposits. Cysts were present mainly on the trigone, the bladder neck and the vicinity of the ureters. Bladder trabeculation and oedema, malposition and dilatation of the ureteric orifices were frequently noted. A large bladder diverticulum was found in 2 patients and cysts were present in the posterior urethra in 1. In 14 children cysts were absent at the time of the first endoscopy but appeared later; the average time interval between the negative and the first positive finding was 32 months,. In 35 patients repeated cystoscopy demonstrated that the cystic changes had persisted, in 24 of these for at least 16 months (at the last cystoscopy they were still present), and in 11 they disappeared, on average, after about 14 months.

Significant bacteriuria was present in 129 patients. The organism most frequently cultured was *E. coli* which was found in 82 patients. Less often, *Proteus mirabilis* (13 cases), paracolon bacteria (11 cases) and Klebsiella (7 cases) were grown. In others a mixed infection was present. 14 children had sterile urine but 10 of these had received antibiotic therapy previously.

Radiological examination revealed the frequent existence of urinary tract abnormalities. Vesico-ureteric reflux occurred in 54 patients. Other lesions encountered included pelvi-ureteric obstruction (7 cases), ureteric duplication (7 cases), renal dysplasia or hypoplasia (6 cases), megaureter (2 cases) and ectopic urethral opening into the vagina (1 case).

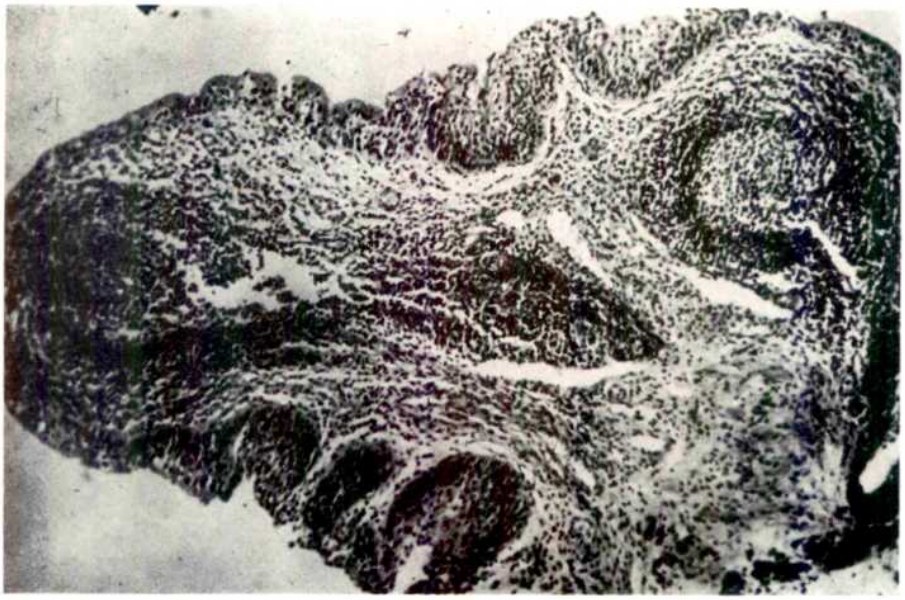

Figure. Histology of biopsy of cystitis cystica. Submucous collection of lymphoid tissue with germinal centres.

Bladder mucosal biopsy was performed in some children in whom the cause of the disease was protracted. Histology revealed nests of lymphoid tissue with germinal centres (Figure).

Discussion and Conclusions

Cystitis cystica in children is due to chronic irritation of the bladder mucosa as a result of urinary infection (Kaplan and King, 1970). In our experience the condition is much commoner in girls than in boys and may occur at any age, even in infancy. Significant bacteriuria is nearly always present and probably always precedes the cystic mucosal changes. The cysts persist for several months and may then disappear. Urinary tract anomalies, especially vesico-ureteric reflux, are commonly present and are important factors in causing the development and the persistence of infection, It is possible that cystitis cystica affecting the ureteric orifices contributes to the occurrence of reflux and the frequent findings of cysts at the bladder neck associated with bladder trabeculation suggests that the mucosal changes may cause some degree of bladder outlet obstruction.

Summary

Cystitis cystica was found at cystoscopy in 157 children between the ages of 9½ months and 14 years. Girls were affected much more often than boys, the proportion being 153 to 4.

Urinary infection, most commonly caused by *E. coli*, was almost invariable.

Urinary tract anomalies, in particular vesico-ureteric reflux, were frequently present.

Histologically, the cysts were composed of submucous aggregations of lymphoid tissue.

Cystitis cystica affecting the ureteric orifices may contribute to the occurrence of reflux and involvement of the bladder neck may produce some degree of vesical outlet obstruction.

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The Authors

G. Vlatković, MD, Professor, Chief of Department of Nephrology, Children's University Hospital Salata, Zagreb.
I. Bradić, MD, Associate Professor, Department of Pediatric Surgery and Urology, University Hospital Rebro Zagreb.
V. Gabrić, MD, Associate Professor, Department of Urology, University Hospital Rebro, Zagreb.
D. Batinić, MD, Assistant.

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Short Case Report

Haemangioma of the Bladder

Bladder haemangioma is a very rare primary bladder tumour. In 1955 Melicow reported 6 cases and in 1969 Fuleihan and Cordonnier added 1 personal case and reviewed 20 others.

The main clinical feature is gross recurrent haematuria; there may be haemangiomata located elsewhere.

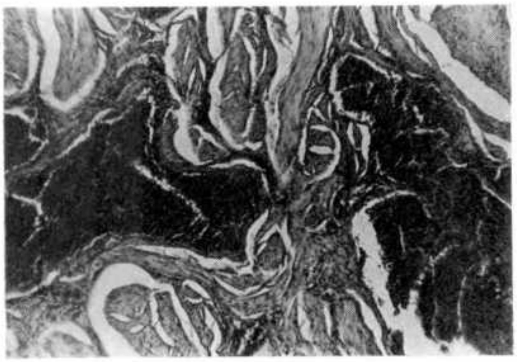

Fig. 1.

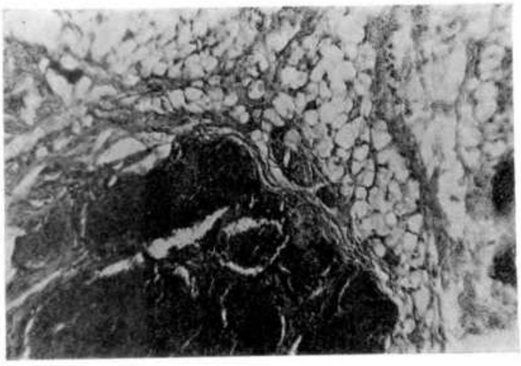

Fig. 2.

Case Report

7 year old girl. At age of 5, large haemangioma of the perineal region was resected. Gross haematuria of 1 month's duration. Cystoscopy: numerous disseminated small bluish tumours on the dome.

Segmental cystectomy including perivesical tissue and a large portion of the peritoneum for haemangioma of bladder wall which extended to the subperitoneal periurachal venous network.

Histology: haemangioma of cavernous type of the bladder musculature (Fig. 1), involving the perivesical tissues (Fig. 2).

Uneventful recovery. 3 months later, rectal bleeding of unknown origin (rectosigmoidoscopy normal).

Comment

Although benign in nature, bladder haemangioma requires treatment, because of recurrent haematuria, preferably by segmental cystectomy, since transurethral resection, fulguration or radiotherapy are both risky because of haemorrhage and often incomplete. Follow-up of patient is mandatory.

E. Proca
Department of Urological Surgery, Postgraduate Medical School, Fundeni Hospital, Bucharest

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The Clinical Diagnostic Value of the Carcinoembryonic Antigen (CEA) in Haematuria

A. G. TURNER, S. CARTER, E. HIGGINS, R. W. GLASHAN and A. MUNRO NEVILLE

Royal Marsden Hospital, Fulham Road, London; Institute of Cancer Research, Chester Beatty Research Institute, Fulham Road, London; and Huddersfield Royal Infirmary, Huddersfield

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The carcinoembryonic antigen (CEA) is a glycoprotein first found in extracts of human colonic cancer and the colon of human foetuses during the first trimester of pregnancy by Gold and Freedman (1965*a*, *b*). Further studies by other workers have shown that CEA is present at trace levels in the plasma of normal subjects and may be raised in a wide variety of neoplastic and non-neoplastic conditions (see review by Neville and Cooper, 1976). Thomson *et al.* (1969) initially considered that plasma CEA elevations were found only in cases of endodermally-derived carcinomas. As the bladder is, in part, endodermally-derived, this led Hall *et al.* (1972, 1973) to look for raised plasma and urine CEA levels in patients with urothelial carcinoma and to assess whether monitoring of plasma and/or urine CEA levels would be of value in the diagnosis and management of urothelial carcinoma.

Plasma levels were found to have little relation to the presence or clinical stage of the tumour and they concluded that a raised plasma CEA was of no value in the detection of urothelial carcinoma (Hall *et al.*, 1973), a finding recently supported by Fraser *et al.* (1975). While CEA or CEA-like substances were present in the urine of normal subjects (Neville *et al.*, 1973), Hall *et al.* (1972, 1973) found elevated urinary levels in 66% of patients with established overt urothelial carcinoma but not malignant tumours at other sites associated with raised plasma CEA levels, unless there was direct tumour invasion of the urothelium. In 2 subsequent studies, these data have been largely confirmed (Coombes *et al.*, 1975; Fraser *et al.*, 1975). Unfortunately, some patients with urinary infections were found to have raised urinary CEA levels. In view of the above findings, a prospective study was initiated by the Medical Research Council and the Department of Health and Social Security to assess whether plasma and urinary CEA levels in patients presenting with haematuria would help to differentiate between benign and malignant conditions.

Patients and Methods

The trial was composed of patients presenting with haematuria to the Urological Department of the Royal Marsden Hospital, London, and Huddersfield Royal Infirmary, over a period of 18 months. A total of 216 patients were admitted, 159 males and 57 females. Urothelial carcinoma was assessed according to the recommendations of the International Society of Urology on TNM Classification of Urological Tumours (UICC) 1974 (Wallace, Chisholm and Hendry, 1975). Each patient, in addition to a full history and clinical examination, was investigated as follows:

(i) mid-stream urine for bacteriological examination; urinary infection was diagnosed if there were greater than 25 WBC per HPF and greater than 100,000 organisms on urine culture;
(ii) urine for cytology;
(iii) intravenous pyelography;
(iv) cysto-urethroscopy and bimanual examination under general anaesthesia;

Table I

Diagnosis of Cases presenting with Haematuria

Diagnosis	No. of cases
1. Urinary tract infection with NO evidence of urothelial carcinoma	38 (18%)
2. Urothelial carcinoma	93 (44%)
3. Urological conditions with NO evidence of urinary infection	82 (38%)
Benign prostatic hypertrophy	22
Infective*	36
Calculous disease	7
Non-urothelial malignant disease	4
Extra-urinary tract disease involving the urinary tract	2
Trauma	1
Miscellaneous	10

* This is a group of patients in whom the haematuria occurred in association with the clinical symptomatology of a urinary infection but who were not referred to the Urological Unit until the infection had been treated and the haematuria ceased. Other investigations showed no abnormality to account for the haematuria.

Table II

Levels of Plasma and Urinary CEA in Patients presenting with Haematuria and Diverse Pathology

Conditions	No. of patients	Plasma CEA*		Urinary CEA*	
		Normal	Raised	Normal	Raised
Infective	38	38	0	13 (34%)	25 (66%)
Urothelial carcinoma	93	89	4	14† (39%) 36‡ (63%)	22† (61%) 21‡ (37%)
Other urological conditions	82	80	2	77 (94%)	5 (6%)

* Plasma CEA: normal <40 ng/ml; raised >40 ng/ml. Urinary CEA: normal <35 ng/ml (male); <110 ng/ml (female).

† Tumour and urinary infection present.

‡ Tumour and NO urinary infection present.

(v) urine and plasma for CEA, which was assayed as outlined by Hall *et al.* (1972, 1973) and Laurence and Neville (1972), respectively.

On the basis of our previous experience (Hall *et al.*, 1972, 1973), urinary CEA values, <35 ng/ml in males and <110 ng/ml in females, are considered to be normal. The higher normal values for females is taken as no special precautions were used in collection of the urine specimens and contamination with vaginal and cervical secretions may influence the level of CEA or CEA-like material in the urine. In both sexes, plasma levels <20 ng/ml are normal, 20-40 ng/ml suspicious and >40 ng/ml abnormal (Hall *et al.*, 1972, 1973; Laurence and Neville, 1972). For clinical diagnostic purposes, however, as only one reading is being studied, we have taken the cut-off point as

Table III

Plasma and Urinary CEA in Urothelial Carcinoma as a Function of the Tumour Stage

Plasma CEA

Stage	No. of cases	Normal*	Raised*
TIS	3	3	0
T1	29	28	1
T2	13	13	0
T3	24	21	3
T4	6	6	0
TX	11	11	0
GO	7	7	0

Urinary CEA†

Stage	No. of cases	Normal*	Raised*
TIS	2	1	1
T1	22	14	8
T2	7	4	3
T3	11	7	4
T4	5	2	3
TX	8	7	1
GO	2	1	1

* For normal values, see Table II.
† Only cases with non-infected urines considered.

40 ng/ml. The grey area of 20-40 ng/ml is avoided in this way as such levels may be found in inflammatory disease alone.

Results

A definitive diagnosis was made in 213 cases. Only 3 (less than 2%) of the cases presenting with haematuria remain undiagnosed even after repeated follow-up investigation. This percentage is lower than previous similar studies of haematuria (Burkholder *et al.*, 1969; O'Reilly, 1974). Undiagnosed cases were excluded from the trial. The various diagnoses of the 213 patients are shown in Table I, and their plasma and urinary CEA levels in Table II. Two cases without urothelial carcinoma were found to have a raised plasma CEA. One case was a carcinoma of cervix invading the urinary tract locally, while the other showed no evidence of malignant disease on investigation. The cause of the haematuria occurred synchronously with the symptoms of urinary infection and this was treated prior to referral to the Urological Unit.

As may be seen, urinary infection frequently results in raised urinary CEA levels (Table II). Of the 5 cases without evidence of either urothelial malignancy or infection, and a raised urinary CEA, the cause of the haematuria was considered to be infective in 4 cases. The patients experienced haematuria coincidentally with the clinical symptomatology of a urinary infection and this seemed to have been adequately treated prior to referral to the Urological Department. Urinary cytology in each of these cases showed no evidence of malignant cells. The fifth case was found to have a ureterocoele and again urinary cytology was normal. In all cases no other pathology was found after full investigation of the urinary tract.

Urothelial carcinoma may be divided according to its stage and spread and the results are shown

Table IV

Results of Urinary Cytology as a Function of a Urinary Infection in Cases of Urothelial Carcinoma.

	No. of cases	Cytology		
		Positive	Suspicious	Negative
Infected*	32	24	2	6
Not infected†	53	36	2	15
Totals	85	60	4	21

* No cytology results on 4 cases.
† No cytology results on 4 cases.

Table V

A Comparison of Urinary CEA and Urinary Cytology in Cases with NO Urinary Infection with Histologically Proved Urothelial Carcinoma.

Cytology	No. of cases	Urinary CEA	
		Normal*	Raised
Positive	35	20	16
Suspicious	2	0	2
Negative	15	11	4
Totals	53	31	22

* For normal values, see Table II.

in Table III. There appears to be little or no consistent correlation between the stage of the disease and the urinary CEA levels. Almost all of the patients, irrespective of stage, had normal plasma CEA levels.

Cytological examination of the urine was performed on all patients. 3 patients who had urinary infections at the time of haematuria were found to have malignant cells in the urine, but despite repeated examination of the urinary tract, there is no clinical evidence of carcinoma of the urothelium. 2 further cases in whom the haematuria was associated with infection had suspicious cells on cytological examination but these also do not show any clinical evidence of carcinoma. The plasma and urinary CEA levels of these 2 patients are normal. All 5 cases remain under observation.

Of the 93 cases of urothelial carcinoma, the results of cytological examination are shown in Table IV. A diagnostic accuracy of 70% was achieved.

The usefulness of adding urinary CEA results to cytology in cases with non-infected urine is shown in Table 5. In only 6 cases out of 53 does CEA add significantly.

Discussion

The purpose of this prospective study was to ascertain whether estimation of the plasma or urinary CEA level in patients presenting with haematuria was of diagnostic or differential diagnostic value. Any further measurement that may be of value in the earlier diagnosis deserves evaluation and assessment, not only as a sole test, but also in conjunction with, and in relation to, already established and proven diagnostic methods. Hall *et al.* (1973) studied plasma CEA in relation to urothelial carcinoma and found only 2/73 patients had raised plasma CEA levels. Both patients had deeply invasive tumours. Later, Coombes *et al.* (1975) found that 13/76 (17%) and 11/33 (33%) of patients with local or disseminated disease, respectively, had raised plasma CEA levels, while Fraser *et al.* (1975) found that 7/90 (8%) of patients with active disease had raised levels. Our present data agree with these findings, 4/93 (4%) had raised levels and 3 had invasive tumours. The consensus, therefore, is that a single plasma CEA reading is of no value in the diagnosis of urothelial carcinoma. However, if it is raised, it may indicate invasive tumour, or the presence of metastatic disease.

The CEA assay for urine measures local CEA-like activity and chemical studies have revealed a variety of cross-reading components (Neville *et al.*, 1973; Nery *et al.*, 1974) which may reduce the accuracy of the urinary CEA value as measured by radioimmunoassay (Coombes *et al.*, 1975). It has been shown that the level of urinary CEA and CEA-like materials are not related to plasma CEA levels (Karakousis, Holyoke and Chu, 1975) or the bacterial content of the urine (Hall *et al.*, 1973). It is concluded, therefore, that the urinary CEA and CEA-like materials are released from the inflamed or malignant transitional epithelium, a conclusion which has been corroborated recently by the demonstration, by immunoperoxidase methods, of CEA in normal and malignant epithelium (Heyderman, 1976, personal communication).

In this series, with proven urinary infection, and in the absence of urothelial malignancy, the urinary CEA levels were raised in 63% of patients in accordance with previous reports (Hall *et al.*, 1972; Coombes *et al.*, 1975). 5 cases without evidence of infection or tumour were found to have raised urinary CEA levels but in 4 of these, a history strongly suggestive of urinary infection coincident with the episodes of haematuria was given.

Evaluation of urinary CEA as a diagnostic parameter for urothelial carcinoma must be made in comparison to the established parameters, particularly urinary cytology, which alone has been shown to be positive in about 75% of cases (Foot *et al.*, 1958; Schoonees *et al.*, 1971; Coombes *et al.*, 1975), a figure comparable to the present series (Tables IV and V).

Urinary infection vitiates the use of urinary CEA as a diagnostic parameter. Thus, for a large number of cases (34 (39%) in this series), the use of urinary CEA is negated and the clinician has to depend solely on urinary cytology and cysto-urethroscopy.

A comparison of urinary cytology and urinary CEA can only be considered in the group without evidence of urinary infection. Of this group of 53 cases, 35 had a positive cytology. Of the 17 with negative cytology, 6 had raised urinary CEA levels. Hence, CEA adds little to the initial diagnosis and also, when raised, seems to bear no relationship to the local clinical stage of invasion of the tumour.

These results suggest that neither plasma nor urinary CEA are of value as diagnostic aids to complement established procedures in the detection or staging of urothelial carcinomas.

Summary

Plasma and urinary CEA levels in patients presenting with haematuria have been studied to assess whether they facilitate the differentiation between benign and malignant urothelial conditions. Plasma CEA is of no diagnostic value although, if raised, it may suggest an invasive tumour. Urinary CEA levels are only of value in the absence of urinary infection; even then, only 37% of the cases with overt urothelial tumours had raised titres. A knowledge of the urinary CEA level, therefore, would seem to contribute little to the diagnosis of patients presenting with haematuria and all patients must still be investigated by the conventional techniques of urinary bacteriology, cytology, intravenous pyelography and cystourethroscopy.

We would like to express our gratitude to Dr P. Trott of the Royal Marsden Hospital and Mr A. Riley of

Huddersfield Royal Infirmary for their cytological studies, and to Mr Wallace, Mr Grant Williams and Mr Hendry for permission to study their cases.

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The Authors

A. G. Turner, FRCS, Lecturer in Urology, Institute of Cancer Research and Hon. Senior Registrar, Royal Marsden Hospital.

S. Carter, Technician, Institute of Cancer Research.

E. Higgins, DObstRCOG, Clinical Assistant, Huddersfield Royal Infirmary.

R. W. Glashan, FRCSEd, FRCSGlas, Consultant Urologist, Huddersfield Royal Infirmary.

A. Munro Neville, MRCPath, Professor of Experimental Pathology, Institute of Cancer Research and Hon. Consultant Pathologist, Royal Marsden Hospital.

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A Double-blind Trial of the Effects of Candicidin on Patients with Benign Prostatic Hypertrophy

P. H. ABRAMS
Clinical Investigation Unit, Department of Urology, Bristol

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Steroidal preparations, both oestrogens and androgens, have been used to treat prostatic enlargement, but without any definite success. Recently interest has been shown in a group of compounds, the polyene macrolides, which includes amphotericin B, nystatin and candicidin. Candicidin was isolated in 1948 from a strain of streptomyces griscus. In common with amphotericin B and nystatin it is an effective agent against pathogenic yeast and fungal organisms. These properties have resulted in their use in man as antibiotics in the treatment of fungal infections. These antibiotics must usually be given as topical preparations because the absorption of polyene macrolide from the gastro-intestinal tract is negligible. During routine evaluation of these compounds Gordon and Schaffner (1968) found that oral administration of polyene macrolides resulted in a reduction in size and a softening of the prostate gland of the older male dog. Histological studies suggested that these effects were due to a reduction in the glandular component of the hypertrophied prostate. The exact mechanism of action of these compounds has not been established. However, certain studies have shown that one of these compounds, candicidin, reduced the plasma cholesterol levels of chicks and chickens (Fisher, Griminger and Schaffner, 1969; Kwon and Fisher, 1972), and other studies that there is interference with exogenous cholesterol absorption, thereby altering cholesterol transport kinetics (Gordon and Schaffner, 1968; Fisher, Griminger and Schaffner, 1969; Kwon and Fisher, 1972; Micklewright and Trigger, 1974). There is some evidence that the hypertrophied human prostate gland has a higher cholesterol level than normal glands (Swyer, 1942) and it has been suggested that the drugs combine with cholesterol in the gut leading to decreased sterol absorption, lowering of serum cholesterol and consequent re-absorption of cholesterol from the hypertrophied gland (Gordon and Schaffner, 1968).

Nystatin has been evaluated and found to be no better than placebo (Theodorides, Bourke and Griffin, 1972). 3 studies on the effect of candicidin in patients with benign prostatic hypertrophy have been reported (Kliucharev *et al.*, 1972; Orkin, 1974). Each trial was uncontrolled and the results were based on the subjective assessment of prostatic size and the change in residual urine. All authors reported a significant improvement following candicidin treatment.

Patients and Methods

A prospective study was carried out on patients awaiting prostatectomy in the Avon Clinical Area. 62 patients were admitted to a double-blind drug trial of the polyene macrolide, candicidin (Prostatin). Patients with gastro-intestinal disease or an urgent indication for surgery were excluded from the trial. 1 patient who had recently undergone surgery for recurrent peptic ulceration was excluded from the study, as were 3 patients with large residual urines which had led to upper tract dilatation or elevation of the blood area. 1 other patient who had noticed haematuria on 2 occasions prior to investigation was also excluded. With these exceptions those in the trial were consecutive patients referred to the Unit for investigation. Each patient had been recommended for surgery after evaluation of their symptoms, rectal examination and excretion urography. A patient was admitted to the trial only after pressure/flow analysis of micturition had confirmed the presence of a bladder outlet obstruction.

At an initial interview each patient's symptomatology was recorded. 5 symptoms were noted and graded according to severity. Those symptoms were diurnal frequency, nocturia, deterioration in stream, hesitancy and urgency. By addition of the gradings a symptom score was calculated for each patient. A rectal assessment of prostatic size was made and urodynamic investigations performed. The urodynamic investigations consisted of a urine flow rate estimation, residual urine measurement, inflow cystometry, voiding cystometry and a final residual urine estimation.

The urine flow rate and urine volume were measured by an Elema Schonander uroflow transducer (EMT 435) and the rectal and total bladder pressures by Elema Schonander pressure transducers (EMT 34). The data was recorded on a Mingograf multichannel recorder (M 81). Venous blood was taken before and after the treatment period so that any changes in blood chemistry could be demonstrated.

The treatment period was 6 months. The patients were asked to take 2 capsules, 3 times each day with meals. The capsules contained either 50 mg of candicidin or placebo and they were identical in appearance. At the end of the trial the patients' symptoms were recorded, prostatic size assessed and full urodynamic investigations repeated.

Results

10 patients failed to complete the trial—4 patients did not take their capsules regularly, 2 patients failed to attend for final assessment, 1 patient developed severe difficulty in passing urine and was admitted for operation, 1 patient developed acute retention of urine and had a prostatectomy, 1 patient developed significant haematuria and was admitted for investigations and 1 patient complained of intractable nausea related to ingestion of candicidin capsules. This last patient appears to be the only patient who defaulted due to a side-effect of the active drug. 4 patients in the candicidin group and 1 in the control group also complained of nausea whilst taking the capsules. However, the nausea was not of such severity for the patients to complain during the trial period and therefore to be withdrawn from the study. 1 patient developed a severe dermatitis during the study period. However, this patient was in the control group and the dermatitis was thought to be due to a side-effect of sulphonamide chemotherapy given for a urinary tract infection. 1 other patient was known to have developed cystitis during the trial period and was treated by his general practitioner.

Despite the use of local anaesthetic, urodynamic investigations are uncomfortable for the patient. Most patients noted discomfort on micturition for a period of 12 to 36 hours after the investigations and approximately 10%

Table I

Symptomatic Assessment: before and after the Treatment Period

	No. of patients	
	Treatment group (23)	Placebo group (29)
Patient assessment		
Much improved	10 (43%)	13 (45%)
Slightly improved	4 (17%)	5 (17%)
No change	8 (35%)	11 (38%)
Worse	1 (4%)	0
Symptom score assessment		
Improved	9 (39%)	10 (34%)
No change	10 (44%)	15 (52%)
Worse	4 (17%)	4 (14%)
Mean symptom score	5·83→5·17	5·82→4·90

Table II

Urodynamic Data: before and after the Treatment Period

	No. of patients			
	Treatment group (23)		Control group (29)	
Mean values	Before	After	Before	After
Maximum urine flow rate (ml/sec)	7·8	9·2	8·4	8·4
Maximum flow pressure (cm H_2O)	120 0	125 0	141·0	138·0
Residual urine (ml)	59·0	45·0	76·0	67·0

observed some haematuria, although in no case did this persist. In this series of patients no case of a urinary tract infection attributable to the investigations was noted.

52 patients remained—29 were in the control group and 23 in the treatment group. Their ages ranged from 50 to 86 years old with a mean of 66 years. 14 patients were felt to have glands weighing less than 25 gm (of a size suitable for transurethral removal), 25 patients' glands were thought to weigh from 25 to 50 gm and 13 patients were thought to have glands weighing in excess of 50 gm.

Table I shows the patients' evaluation of their treatment together with the changes in mean symptom scores and individual symptom scores for the control and treated groups. If the symptom score had altered by 2 or more points an improvement or deterioration was recorded. Improvement was claimed by 18 (62%) of the control group and by 14 (60%) of the treated group. Symptom scores improved in 10 (34%) of the control group and in 9 (39%) of the treated group. There was no statistically significant difference between the improvement rates of the 2 groups. Each patient was asked whether or not he had experienced any side-effects from the treatment. The only side-effect noted was nausea—4 patients in the treatment group and 1 in the control group complained of this symptom.

No change in prostatic size was noted after the period of treatment. Similarly, no differences in

Table III

Changes in Urodynamic Data following the Treatment Period

	No. of patients	
Changes	Treatment group (23)	Control group (29)
Flow rate (maximum):		
Improved	10 (43%)	12 (41%)
No change	12 (52%)	9 (31%)
Worse	1 (5%)	8 (28%)
Pressure (at maximum flow):		
Improved	5 (22%)	13 (44%)
No change	7 (30%)	8 (28%)
Worse	11 (48%)	8 (28%)
Residual urine:		
Improved	9 (39%)	11 (38%)
No change	2 (9%)	12 (41%)
Worse	12 (52%)	6 (21%)

the haemoglobin, white cell count, serum electrolytes or liver function tests of the 2 groups could be found either before or after the treatment period.

Table II shows the mean urodynamic values for the 2 groups before and after treatment. There were no significant differences between the 2 groups. However, the increase in urine flow rate in the treatment group from 7·8 ml/sec to 9·2 ml/sec did approach statistical significance ($P = 0{\cdot}06$).

The changes for each individual's urodynamic values are shown in Table III. For a change to be recorded an increase or decrease of more than 1 ml/sec for flow rate, more than 9 cm H_2O for pressure and more than 20 ml for residual urine had to be seen. These changes show no significant differences between the 2 groups.

Discussion

This trial has failed to produce any evidence to support the claim that candicidin is an effective and active drug in the treatment of benign prostatic hypertrophy (Kliucharev *et al.*, 1972; Keshin, 1973; Orkin, 1974). Previous trials of this drug have been uncontrolled and the reported results were largely subjective observations. In this study the techniques of urodynamic investigation were used to provide an objective assessment of the possible actions of candicidin.

In both the control and the treated groups more than 60% of patients noted an improvement in their micturition. Similar improvements have been previously reported with both placebo treatment (Castro, 1972) and with no treatment (Craigen *et al.*, 1969). An increase in the mean flow rate of the treated group was noted and is the only finding to suggest that candicidin might be an active drug. The direct relationship between micturition pressure and flow rate is well known. Therefore, the finding of an increase in mean micturition pressure in the treated group partially explains the rise in urine flow rate seen in this group (Table II) .A decrease in the mean residual urine of both groups was observed although these changes were not statistically significant ($0{\cdot}2 > P > 0{\cdot}1$). There is no obvious explanation for this observation but perhaps it suggests a disease process with relative exacerbations.

There appears to be no published evidence as to the rate of progression and natural history of benign prostatic hypertrophy. In this study no significant deterioration in urine flowrate, micturition pressure or residual urine was seen over a 6-month period. This finding, together with the observation that many patients' symptoms improve, suggests that in the absence of an urgent indication for operative treatment patients with benign prostatic hypertrophy may be treated expectantly. This view would be supported by the subjective observation of many surgeons that it is unusual for patients on the waiting-list for prostatectomy to be admitted with acute retention or any of the other complications of benign prostatic hypertrophy.

Summary

62 patients with benign prostatic hypertrophy, leading to bladder outflow obstruction, took part in a randomised double-blind trial. Those patients in the treatment group took 6 capsules of a polyene macrolide, candicidin, each day (300 mg daily dose).

Subjective improvement was noted in both the treated and the control group.

This improvement was not confirmed by pressure flow analysis of micturition.

The results of this trial do not support the view that candicidin is a useful drug in the treatment of benign prostatic hypertraphy.

I should like to thank the urologists of the Avon Clinical Area for permission to study patients under their care and, in particular, Mr J. B. M. Roberts and Mr J. P. Mitchell, Consultant Urologists, for their advice and criticism in the preparation of this manuscript. My appreciation also goes to Miss P. J. Abrams and Miss J. Foster who typed the manuscript and to Pharmax Ltd. who provided support for the study.

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The Author

Paul H. Abrams, FRCS, Research Registrar.

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Short Case Report

Functional Recovery in a Kidney after Prolonged, Complete Ureteric Obstruction

Animal experimental work indicates that recovery of renal function is poor after complete ureteric occlusion for 40 days (Vaughan and Gillenwater, 1971). In humans, pelvic surgery is the commonest cause of partial or complete ureteric obstruction. Return of function after long-term complete obstruction is unusual (Shapiro and Bennett, 1976). This case illustrates the possibilities of late surgical intervention.

E. H., a 42-year-old lady, had a dilatation and curettage performed because of abnormal bleeding. A diagnosis of uterine stromal sarcoma led to a radical hysterectomy on 4th March, 1976. No residual tumour was found. Her postoperative course was uncomplicated. She was entered into a prophylactic chemotherapy protocol for which one of the studies was an intravenous pyelogram. This revealed a non-functioning left kidney. A retrograde pyelogram revealed complete left ureteric obstruction 5 cm above the ureterovesical junction (Fig. 1). Exploration was advised but she refused. Several weeks later she changed her mind. A selective arteriogram was performed confirming a normal-sized left kidney. On 14th May, 1976, 71 days post hysterectomy, exploration and ureteroneocystostomy were performed. The distal ureter was fibrosed and microscopy revealed no lumen. She recovered well and follow-up intravenous pyelogram in August revealed a promptly functioning left kidney with mild calyceal blunting and cortical thinning (Fig. 2).

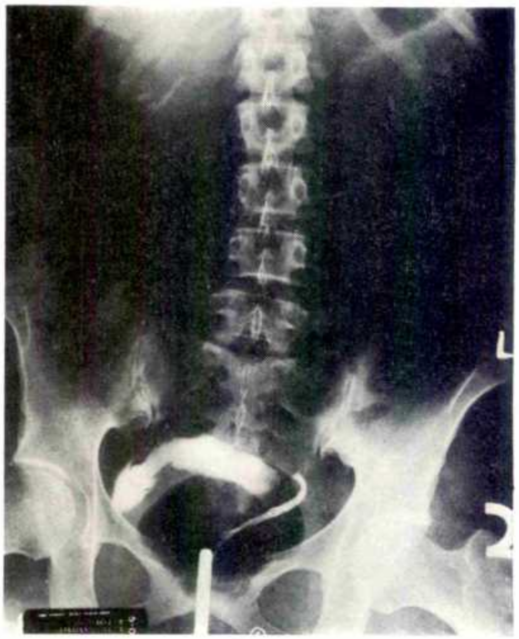

Fig. 1.

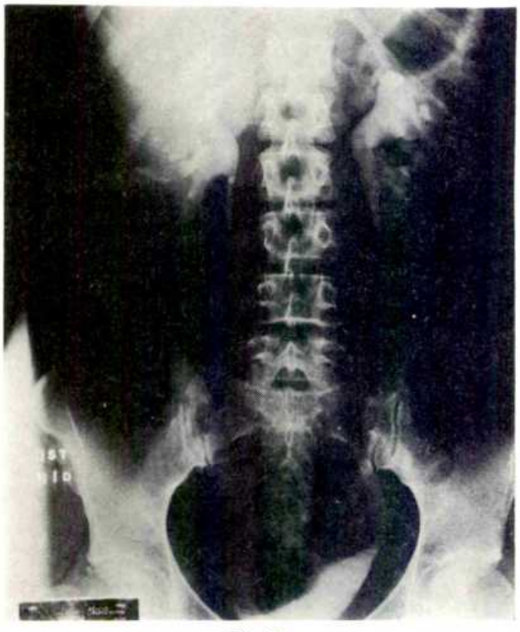

Fig. 2.

BERNARD FALLON, MD
University of Iowa, Department of Urology, Iowa City, Iowa, USA 52242.

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Treatment of Advanced Carcinoma of the Prostate with Estramustine Phosphate

R. NAGEL and C.-P. KÖLLN
Department of Urology, Free University of Berlin, Klinikum Charlottenburg

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There is little to be done for the patient with advanced prostatic cancer after conventional oestrogen treatment has failed to control metastatic bone pain, ureteric obstruction and consequent impairment of renal function. Patients who fail or cease to respond to oestrogen therapy or orchidectomy and who have painful local metastases may respond symptomatically to local radiotherapy (Bagshaw, Kaplan and Sagerman, 1965). Short-term palliation is also possible with corticosteroids that inhibit renal cortical function and at the same time confer non-specific symptomatic benefit (Whitmore, 1956).

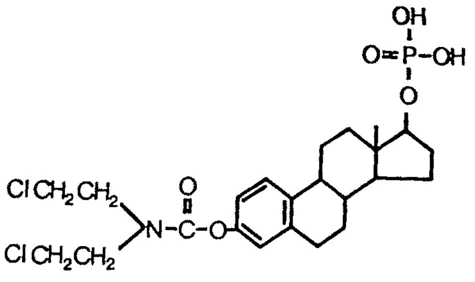
Bilateral adrenalectomy or pituitary ablation by operation or irradiation are of palliative value in a minority of patients with advanced oestrogen-resistant prostatic carcinoma (Straffon *et al.*, 1968; Murphy *et al.*, 1969; Fergusson and Hendry, 1971; Morales, Blair and Steyn, 1971; Murphy *et al.*, 1971; Schoonees *et al.*, 1972). Short-term androgen treatment (Krauss, 1960; Prout and Brewer, 1967) followed by high dose oestrogen therapy has been reported to be of occasional transient benefit.

Cytostatic chemotherapy with cyclophosphamide, nitrogen mustard, thiothepa, 5-fluoruracil or mithramycin has been tried to a limited extent but worthwhile responses have been rare (Rockstroh, Hasselbacher and Barth, 1959; Weyrauch and Nesbit, 1959; Arduino, 1965; Fox, 1965; Arduino and Mellinger, 1967; Flocks and Cheng, 1968; Persky *et al.*, 1970).

Encouraging reports from Sweden (Jönsson *et al.*, 1963; Jönsson and Högberg, 1971; Jönsson, 1971; Nilsson and Müntzing, 1972; Nilsson and Jönsson, 1975) of treatment of advanced carcinoma of the prostate with estramustine phosphate (Estracyt®) stimulated us to study the effect of the drug in 40 patients with metastatic and/or undifferentiated prostatic carcinoma. The study started in 1970 and was restricted to patients unresponsive to, or relapsing after, conventional therapy including oestrogen treatment, castration and radiotherapy. All the patients had tumour progression and symptomatic advanced disease. In 1972 we reported our preliminary observations relating to treatment with parenteral estramustine phosphate (Kölln and Nagel, 1972; Nagel and Kölln, 1972). We now report the results of treatment and the side-effects seen in patients given the drug by mouth over a longer period of time, *i.e.* till June, 1975.

Material and Method

Chemically estramustine phosphate (Estracyt®) consists of nor-nitrogen mustard bound to oestradiol-17-phosphate (Fig.). The compound is dissolved in water for intravenous injection at a dose of 150 mg-450 mg a day. The oral preparation, which is the disodium salt of estramustine phosphate, is a stable, slightly hygroscopic white powder. At physiological pH the compound is in an ionised form, which is inactive *in vitro*. It behaves as a urethane-type nitrogen mustard and is activated by enzymes releasing the alkylating moiety. It has been suggested that the steroid moiety may direct the molecule to hormone-dependent tumours where the alkylating group would be released and direct action on tumour tissue might be more specific (Müntzing *et al.*, 1974).



estradiol-3N-bis-(2-chloroethyl) carbamate-17β-phosphate

Fig.

Table I

Treatment with Estramustine Phosphate in 40 Patients

Intravenously only	15
By mouth only	2
Intravenously followed by mouth only	23

Müntzing *et al.* (1974) found that over 50% of estramustine phosphate given by mouth is absorbed. The compound is excreted as the alkylating and oestradiol metabolites in the urine, bile and faeces.

Since 1970 we have treated 40 patients with inoperable histologically proved prostatic carcinoma with estramustine phosphate. 37 of the patients had metastatic Stage D disease (Flocks, 1971) and 3 patients had Stage C carcinoma on entry.

Average age on entry was 66·1 years (50-83 years). 35 patients had been treated for months or years with oestrogens and/or had undergone bilateral orchidectomy but in all cases progression of the tumour and deterioration of the patient's condition were evident before the start of estramustine phosphate treatment. All patients had metastases, to bone in 24 and to soft tissues and lymph nodes in 26 patients. 23 patients had raised serum acid phosphatase levels. 18 had unilateral or bilateral ureterohydronephrosis.

Histologically 31 patients were shown to have undifferentiated carcinoma of the prostate and 8 patients had only poor differentiation. In a number of patients cytology and biopsy of the prostate were carried out at regular intervals during treatment. A detailed account of this study will be published later.

Dosage

Patients entered to the trial were extensively investigated in hospital, all previous treatment was stopped and estramustine phosphate was started using the intravenous route for the first 3 weeks or longer and then changed to oral treatment with the capsules (Table I).

The initial intravenous dose was 150 mg a day but was increased after a few days to 300 mg a day. An attempt to increase the dose further to 450 mg/day led to gastro-intestinal intolerance, so that 300 mg is now taken as the maximum intravenous daily dose.

Oral treatment was started at 560 mg a day (2 × 140 mg capsules, twice a day). Müntzing *et al.* (1974) found the maximum tolerated dose by mouth to be between 20 and 25 mg/kg per day and that 30 mg/kg could not be tolerated for longer than 7 days. Thus our dose of 560 mg a day is about half the reported maximum tolerated dose and is identical with that recommended by Jönsson and Hogberg (1971).

Assessment (Table II)

All patients were assessed at the start of the trial and at regular intervals during the study by:

(*a*) clinical examination,
(*b*) blood chemistry,

Table II

Studies during Estramustine Phosphate Therapy

I. Blood chemistry	II. X-ray and scintiscan	III. Clinical examination and ECG
1. CBC including thrombocytes and reticulocytes	1. Infusion excretory urography	1. Local findings
2. TPT	2. Chest film	2. Voiding symptoms
3. PTT	3. Bone survey	3. Residual urine
4. Fibrinogen	4. Bone scan	4. Oedema
5. Sedimentation rate	5. Lymph node scintigram	5. Angina
6. BUN	6. Lymphangiography	6. ECG
7. Creatine	7. Liver scan	7. Weight
8. CO_2		8. Appetite
9. Acid and alkaline phosphatase		
10. Serum electrophoresis and total protein		
11. Sodium		
12. Potassium		
13. Calcium		
14. Phosphorus		
15. Chlorides		
16. Bilirubin		
17. Bromsulphthalein retention		

(*c*) X-ray and scintiscan,
(*d*) ECG.

In the early part of the trial follow-up examinations were carried out at weekly intervals, later these were extended to monthly or 3-monthly (ECG, bone survey, blood chemistry, etc.). In all patients monthly assessments included analgesic requirement and tolerance of drug.

An objective response was defined as shrinkage of the primary tumour, fall to normal of the serum acid phosphatase level, return to normal of blood urea, disappearance of ureterohydronephrosis, significant reduction in residual urine and reduction or disappearance of bone or soft tissue metastases. Subjective response was defined as improvement in the patient's general condition including gain in weight and appetite and disappearance of bone pain associated with a fall in analgesic requirement.

Results

In 13 patients with advanced metastatic disease intravenous estramustine phosphate was given for a period of less than 2 months. No benefit other than transitory pain relief was seen in any of these patients and all died of widespread metastatic prostatic cancer confirmed at post-mortem.

27 patients were treated for longer than 2 months. 23 of these received the drug first by intravenous injection for at least 3 weeks and then by mouth. 2 patients were treated (for 4 and 8 months) with the intravenous preparation and after this time died of their disease. 2 other patients were treated (for 38 and 42 months) with the capsules only. 1 of these patients died of acute myocardial infarction at the age of 72 years, the second patient is alive and symptom-free 42 months after beginning the therapy.

23 patients were initially treated intravenously for 3 weeks and later by mouth for periods of 2-55 months. 17 of these 23 patients died after an average treatment time of 12·5 months. 6 patients are alive and well after an average treatment period of 27·7 months (3-55 months).

2 of the 3 patients free from metastases at the start of the treatment died suddenly 44 and 47 months after the start of estramustine phosphate therapy. Both patients died at home and no post-mortem examination was carried

out but myocardial infarction must be suspected as the cause of death. It has to be stressed, however, that the ECG taken 6 months before showed no signs of deterioration of the myocardial status and both patients, 68 years old at the time of their death, had been on this drug for almost 4 years. The third patient is alive and free from metastases at 55 months.

Metastatic bone pain was reduced during the first fortnight of treatment in about 40% of the patients. If no improvement was evident after this time increasing the dose of estramustine phosphate produced no additional benefit. Reduction of blood urea, improvement in micturition and general subjective benefit were seen in several patients. In 5 there was significant reduction of ureterohydronephrosis; in 2 who had had urinary retention on entry there was complete elimination of residual urine after a few weeks' treatment with the drug.

In 15 of the 23 patients with significantly raised serum acid phosphatase at the start of treatment there was prompt return to normal levels. 2 patients had extensive metastases in the corpora cavernosa and corpus spongiosum at the start of treatment. In 1 there was remarkable regression of the metastases and relief of voiding problems before he died 5 months later of his carcinoma of the prostate. However, no obvious improvement was seen in the second patient.

An especially dramatic if temporary success was the fact that in a 52-year-old patient a metastatic paraplegia improved during estramustine phosphate therapy for 6 months so that the patient was able to walk again. However he died 8·5 months later of his prostatic cancer (Table III).

Toxicity (Table IV)

Thrombophlebitis, a frequently reported side-effect of intravenous estramustine phosphate in the area of injection,

Table III

Results of Estramustine Phosphate Therapy

	N=40*
Improvement of metastatic bone pain	10/23
Improvement of azotaemia	5/9
Improvement of hydronephrosis	5/18
Normal acid phosphatase	15/23
Free of residual urine after urinary retention	2/2
Free of metastases in corpora cavernosa/spongiosa	1/2
Improving metastatic paraplegia (52-year-old) for 6 months	1

* In some patients several of these results were achieved.

Table IV

Estramustine Phosphate Side-effects

	Estramustine phosphate parenteral	Estramustine phosphate oral
Nausea, vomiting	2	0
Diarrhoea	2	0
Transient nausea	5	5
Liver retention (Bromsulphthalein)	6	1
Thrombophlebitis	3	0
Haemopoietic system	0	0

was seen in 3 patients only. This complication can be avoided by using a small gauge needle (No. 12) and careful technique as was shown by personal experience.

A number of patients complained of perineal pain or itching after intravenous injection especially during the first few days. The sensation lasted for a few minutes. It was not reported by patients receiving the drug by mouth.

We encountered no significant haematological abnormalities and thrombocytopenia was not seen in any of our patients treated for up to 55 months, nor was there any evidence of adverse effect on clotting mechanisms. This confirms the reports of other authors of lack of haemopoietic toxicity (Alfthan and Rusk, 1969; Anderes *et al.*, 1971; Jonsson and Högberg, 1971; Rüedi and Bonvin, 1975).

Nausea and vomiting occurred in only 2 patients receiving the standard dose (300 mg per day) of intravenous estramustine phosphate. However, transient nausea during the first few days of treatment was commoner and complained of by 5 patients receiving the drug intravenously and by 5 taking the drug by mouth. In general, nausea is transitory and easily controllable by temporary dose reduction or administration of antacids or short discontinuation of the drug.

Müntzing *et al.* (1974) reported transient nausea in 9 of 11 patients receiving oral estramustine phosphate at the higher dose of 10-30 mg/kg. Undoubtedly the dose-limiting toxicity is gastro-intestinal and 2 of our patients suffered from severe diarrhoea.

Raised serum bilirubin and increase in bromsulphthalein retention was noted in 6 patients, 5 of whom were being treated with intravenous estramustine phosphate. The other had been taking the drug by mouth for 7 months after his initial intravenous course before the rise in bilirubin was noted. Liver function studies promptly returned to normal in these 5 patients when the drug was discontinued. In our preliminary report we referred to the possible temporary hepatoxic effects of estramustine phosphate and recommend that liver function tests should be carried out regularly on patients under treatment with the drug (Nagel and Kölln, 1972). Müntzing *et al.* (1974) found no evidence of liver toxicity in patients receiving 10-30 mg/kg by mouth but Jönsson and Högberg (1971) reported 2 cases in which bilirubin returned to normal when the drug was stopped.

Patients with congestive heart failure and with angina pectoris should be carefully observed. 3 of our patients died suddenly during the 38th and 47th months of treatment, 2 of them presumably of cardiac disease. However, only the first patient had an autopsy which revealed myocardial infarction as cause of death. These patients were 72, 68 and 68 years old at the time of death. 2 other patients complained of an increased frequency and severity of angina during the treatment with estramustine phosphate.

Discussion

Encouraging results of treatment of advanced carcinoma of the prostate with estramustine phosphate have been reported from Scandinavia and elsewhere. The drug has been recommended principally for the treatment of patients with tumours resistant to or relapsing after conventional oestrogen therapy (Alfthan and Rusk, 1969; Anderes *et al.*, 1971; Jönsson and Högberg, 1971; Andersson, 1975).

In our study of treatment for up to 55 months of 40 patients with inoperable prostatic carcinoma, both the intravenous and the oral form of estramustine phosphate were well tolerated and we found no evidence of haematological toxicity.

Occasional transient hepatotoxicity was encountered but was quickly reversed when drug treatment was stopped. Gastrointestinal toxicity is easily controlled by dose reduction or interruption or by antacids.

Conclusions

We consider estramustine phosphate worthy of trial in patients with prostatic cancer resistant to oestrogens or with relapsing metastatic disease. The regimen of treatment recommended is initial intravenous therapy at a dose of 300 mg estramustine phosphate a day for 3 or more weeks followed by oral administration of the drug at 280 mg twice daily provided there is good gastrointestinal tolerance. Liver function studies should be carried out at regular intervals.

Summary

40 patients with inoperable, histologically proved carcinoma of the prostate were treated with estramustine phosphate. 35 patients had progressive, symptomatic, metastatic disease unresponsive to conventional oestrogens and/or castration.

Estramustine phosphate was given intravenously initially at a dose of 150 mg/day increasing to 300 mg/day. After 3 weeks or more oral therapy was substituted in 23 patients at a dose of 560 mg/day.

Of 23 evaluable patients given the drug by both routes, 17 died after a mean treatment period of 12·5 months and 6 are alive and well after a mean treatment period of 27·7 months.

The cause of death in 2 patients was probably, and in a third certainly, due to myocardial infarction. The other 31 deaths were due to carcinoma of the prostate.

18 patients showed transient toxic side-effects.

No haematological abnormalities were found during treatment.

An attempt at active treatment with estramustine phosphate in patients with prostatic cancer is justified when the disease is resistant to treatment with conventional oestrogens.

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The Authors

R. Nagel, MD, Professor of Urology.
C.-P. Kolln, MD, Assistant Professor (now at 1300 Second Av. S.E., Cedar Rapids, Iowa 52403, USA).

Requests for Reprints to: Professor Dr R. Nagel, Free University of Berlin, Klinikum Charlottenburg, Spandauer Damm 130 D-1000 Berlin 19.

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Suggested Project For Urological Research

Does Ureteric Reflux protect against Calculus Formation?

Urinary tract stone is a frequent disease and has been the subject of numerous articles in the urological literature. The association of urinary calculi and infection is one of the axioms of urology. During the past 20 years vesical-ureteral reflux has been recognised as a frequent and significant urological disease entity as well: it too is frequently associated with infection.

I have been struck by the infrequency with which I have seen these two conditions associated in my own experience. Indeed, little has appeared in the literature concerning the association of these two diseases. The obvious question, therefore, is "Is it possible that vesical-ureteric reflux confers protection against the formation of renal calculi?" Skinner and Goodwin (1975) and others have treated recurrent stone-formers by substitution of ileum for ureter. Conceivably the improvement that occurs is not merely the result of the larger calibre conduit but may be a function of the reflux that is usually engendered by these procedures.

This question could be answered by a relatively simple project. A foreign body would be implanted into the renal pelvis of the experimental animal to provoke stone formation A piece of zinc would be suitable, or perhaps discs cut from a staghorn calculus; these, of course, must be sterilised, weighed, and made sufficiently large so as to ensure their retention in the renal pelvis. Then, after allowing time for the pyelotomies to heal, the ureteric vesical valve on one side would be rendered inoperative; in this way a single animal would have a built in control.

Follow-up examination could be done radiographically and finally by comparing the weight of the implanted stones on the two sides. This relatively simple experiment with a small number of animals should suffice to indicate whether further research in this direction is justified.

Summary

The infrequent association of reflux and kidney stone suggest the possibility that reflux may in some measure protect against stone formation. A simple animal experiment is proposed which should indicate whether this assumption is valid.

DAVID H. KUNTZ, MD
8540 Sepulveda Boulevard, Los Angeles, California 90045

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Book Reviews

Urology. Edited by John Blandy. Volumes 1 and 2. pp. 616 and 616. Oxford: Blackwell Scientific Publications, 1976. £46·00.

Publication of this book has been eagerly awaited for a long time. It fills an inexplicable gap in British urological literature which has until now lacked a comprehensive textbook. Furthermore, as Professor Blandy has a reputation for not accepting a statement as true simply because someone has made it before, we have expected a frankness of approach which could discard some of the rubbish which tends to be solemnly passed from book to book. We have not been disappointed.

The layout is novel. Nearly a third of the book is blank paper, the print being confined to the medial two-thirds of the page with some illustrations and captions penetrating the lateral border. The idea is to produce a book which is easy to read. Taken with a very high quality of production, the result is admirably successful and likely to be copied in the future. Here and there, however, there is some rather irritating dissociation of illustrations, captions and text. One disadvantage of this format is an enormous increase in weight, but apparently the additional cost of all the blank paper is only a few pence per volume. One must, as ever these days, comment on the price, which is excessive and must inevitably limit its distribution.

Contributions are all British. The standard of writing is high, and uniformly clear, and the concise style of all the authors allows the presentation of as much factual information as many of the more verbose textbooks currently available. A reasonably comprehensive bibliography at the end of each section covers the world's literature and identifies the more important sources. Professor Blandy is to be congratulated on an excellent editorial job.

The book comes in two volumes. Volume 1 deals with the urologists' armamentarium, the kidney, the renal pelvis and ureter. Volume 2 covers the bladder, prostate and urethra, urinary fistulae and diversion, the male genitalia and the adrenals. At long last, the traditional and valueless introductory chapters on anatomy and physiology are omitted.

Division of the work into these 8 anatomical parts looks impressive in the table of contents, but unfortunately creates some anomalies which detract somewhat from the value of the many welcome innovations. For example, the chapter entitled "Carcinoma of the Urothelium" deals only with bladder cancer, paying lip service to the concept of a pan-urothelial disease. Tumours of the upper urothelium are to be found in "The Kidney"—not even in "The Renal Pelvis and Ureter", and urethral tumours are but an afterthought to urethroplasty. Similarly the aetiology and therapy of urinary infection and the management of genito-urinary tuberculosis are considered with "The Kidney" alone, and urinary obstruction and renal function are included in the "Renal Pelvis and Ureter".

"The Urologist's Armamentarium" is a misnomer. One chapter describes endoscopic instruments and diathermy, 4 are concerned with radiology. It might be better entitled "Urological Investigations" and include radioisotope studies of the kidney which is at present elsewhere, and perhaps methods of investigating ureteric and bladder function. "Cystography" makes no mention of what is surely its most important use, in the evaluation of bladder function.

Disease of the kidney and ureter are comprehensively and well described and it would be invidious to pick out any particular chapter as superior. Omissions are few and trivial, and perhaps the one topic which is curiously placed in "Injuries to the Ureter" which surely deserves rather more prominence and amplification is the subject of vesico-ureteric reflux in the adult. The problem of reflux is more fully discussed in the chapter on "Congenital Anomalies", and it seems a pity to separate two aspects of the same functional disorder.

How much operative surgery should be included in a book of this nature is debatable. The amount of operative detail given is variable and inconsistent. Operations on the kidney are fully described, but are scattered throughout the text and hence there is some repetition. The beginner wishing to loop up these procedures would have to work hard with the index. Elsewhere, operations are described mainly in outline only.

Discussion of the "Frequency-Dysuria Syndrome" in a separate section from that containing disorders of the female urethra misses the main point of one of urology's vexed clinical problems, as does the chapter in question.

This is the only real disappointment. The opportunity to deal decisively with this common but confusing problem has been lost for at the outset the author calls it "cystitis" and proceeds by failing to distinguish satisfactorily the bacterial from the abacterial, the honeymoon from the menopause and the pathological from the functional. The two chapters in Volume 1 on Urinary Infections contribute to this error in that they fail to separate clearly "frequency and dysuria" from infection. Neither do they identify the dysfunctions of the lower urinary tract which should be sought and corrected to treat infection when it is present and prevent a recurrence.

The chapter on the function of the bladder is masterly in its simplicity and brevity, and the contributions on the bladder in disorders of the nervous system, cystoplasty, the benign prostate, injuries and urethral stricture are particularly useful.

Add to these the inclusion of subjects such as renal transplantation, sexually transmitted diseases, intersex, male infertility and adrenal surgery and you have the best major urological textbook currently available.

This book is a must for every apprentice urologist for some of whom overtime payments will ease the burden of the price tag.

D. M. E. and R. R. H.

Lecture Notes on Urology. By John Blandy. Pp. 326. Oxford: Blackwell Scientific Publications 1976. £5·60.

Until recently there has been no adequate elementary textbook of urology which could be recommended to students and housemen. A number of recent publications have filled this gap, and this latest addition to the "Lecture Notes" series will undoubtedly become standard reading for the medical student. There should now be no need to rely on the misleading and inadequate information to be found in some of the popular general surgical textbooks.

As usual, Professor Blandy writes clearly, concisely and pleasantly. The text is illuminated by many thumbnail sketches, many of which rival Hamilton Bailey's ability graphically to summarise a good deal of information in one memorable sketch. A short bibliography at the end of each chapter is more adequate for the beginner.

It is always a pleasure to review a book which repeatedly expresses views which coincide exactly with one's own—it must be good! However, three points deserve comment. It is surprising not to find details of how to pass a catheter. Many nocturnal struggles ending in total defeat of both patient and houseman might be avoided by clear instructions on how to anaesthetise the urethra. Ignorance of this is surely the most common cause of failure. Secondly, we repeatedly hear plaintive cries from our non-surgical colleagues that the patient has "prostatic" symptoms but "his prostate is not enlarged". The irrelevance of prostatic size could be stressed more than it is, and perhaps the observation made that we are probably dealing with more than one pathological condition in the disease labelled loosely as "prostatism".

Finally, and unfortunately, Professor Blandy does not give an adequate account of the commonest problem in urology. Nor does any other urological textbook. The patient who presents with frequency and dysuria is inevitably labelled "cystitis" and given antibiotics. Our ignorance of this common problem may be profound, but we can cure many of them—without antibiotics—and it is surely now essential to give some elementary guidance on the immense amount of work which has been published on bladder physiology.

Nevertheless, these "Lecture Notes" succeed admirably in their intent and should be regarded by the student as an essential possession. Not just on the Library shelves. At £5 60 with a high standard of production, the book is a bargain at present-day prices.

D. M. E.

Dialysis, Transplantation and Nephrology. *Edited by* J. F. Moorhead, G. Mion, R. A. Baillod. (*Proceedings of the European Dialysis and Transplant Association, 1975, Vol. 12*). Pp. 638, well illustrated. Tunbridge-Wells: Pitman Medical, 1976. £16·50.

The Annual Meeting of the E.D.T.A. now attracts participants from all over the world, including the U.S.A. and Australia, although mainly devoted to European work. Because of the wide representation the proceedings now provide a valuable update on a considerable part of nephrology.

The Report of the Registration Committee provides a valuable guide for those surgeons and physicians directly involved in dialysis and transplantation to the general level of results obtained against which to set their own achievements. There are limitations in the figures quoted which are inevitable in any multicentre retrospective study such as this and the authors cannot be held responsible for these. Thus they find that the presence of cytotoxic antibodies indicates a poor outcome for a renal transplant, while in individual centres the reverse has been shown, this difference being attributable to variability in the quality of laboratory techniques. Similarly HLA typing come out as being of only marginal importance. This may be partly due to faulty typing techniques, but may also arise from the failure to distinguish between the HLA-A and HLA-B loci. A minor criticism in this section is that hypertension is not listed as a cause of end-stage renal failure and this must lead to some distortion of the overall figures, since hypertension must be being included in some other group.

The "Editorials" Section in the book is useful in giving an overview of a subject which is of more lasting value than the selection of papers which are of more transient interest and are usually published in more detail elsewhere anyway. The inclusion of the discussion following the papers is welcome, however.

Many useful papers are included covering a wide spectrum ranging from practical tips on peritoneal dialysis to complex papers on the mechanisms regulating sodium absorption in the nephron.

This volume is well edited and interesting and is to be recommended to physicians and surgeons working in the field of dialysis and transplantation. In addition it contains a few pearls for the more physiologically orientated general physician and endocrinologist.

R. W.

Renal Insufficiency. Wurzburg Symposium, Nov. 1974. Edited by A. HEIDLAND, H. HENNEMANN and J. KULT. Pp. 292, 188 figures, 45 tables. Stuttgart: Thieme, 1976. Price DM48.

It used to be said in the field of research in chemistry that if you had an "original" idea you would usually find from the German literature that someone else had worked it through 10 years earlier. This book gives one the impression that the same may apply in medicine in the future.

Although it is almost 2 years since the conference of which this book is the proceedings, the material is fresh since the time interval does not greatly exceed the time required to prepare, submit and have original work published by other channels. There are some parts where the English is poor and I would have thought that the inclusion of an editor whose native tongue was English would have been a worthwhile investment.

This minor criticism apart, the idea of publishing the proceedings in English was a good one, opening a large body of German work to the non-German reading English-speaking medical world. There are excellent contributions on the role of renin in the hypertension of parenchymatous renal disease and also on the value of renal vein renin levels following hydralazine stimulation in the assessment of renal artery stenosis.

Besides renal hypertension there are excellent sections covering uraemic toxins, protein and amino acid metabolism, dialysis and the extrarenal manifestations of uraemia. One disappointment is failure to print the discussion which presumably followed each paper at the Symposium, although the discussion must present considerable editorial difficulties it does help to put a piece of work into perspective.

The book is to be recommended to renal physicians rather than surgeons but the first section will also be of interest to the general physician with an interest in hypertension.

R. W.

Radionuclide Studies of the Genito-urinary System. Edited by LEONARD M. FREEMAN and M. DONALD BLAUFOX. Pp. ix+220 with 106 illustrations. New York: Grune and Stratton, 1976. £7·55.

This book is a hard-back reprint of the January and April, 1974, quarterly issues of "Seminars in Nuclear Medicine" in which the editors, by inviting contributions from workers in Germany, France, UK and Canada as well as the USA, have tried to present a broad view of the field.

The first half of the book, loosely entitled "Fundamental Principles", is a collection of reviews of materials and methods. In the first article the vast assortment of radiopharmaceuticals which have been developed over the years are neatly evaluated and categorised on the basis of their suitability for measuring glomerular filtration rates, renal plasma flow, renal blood flow, renal morphology and perfusion; a useful table of radiation doses is included. The second article concludes that radioisotope methods have not yet successfully replaced insulin and para-aminohippurate (PAH) clearance for measuring GFR and ERPF despite removing the need for collecting catheterised urine specimens. The radioactive methods for measuring renal blood flow are described. Reynaud considers various ways of quantifying individual kidney function but prefers his Hg uptake method. There is a review of the various techniques and physiological models used in attempting to analyse radioisotope renograms.

The second half of the book is devoted to reports and reviews of clinical applications of the various radioisotope methods in the study of renovascular hypertension, traumatic injuries, space-occupying lesions, transplanted kidneys, obstructive uropathy and cystography.

These articles were originally published well over 2 years ago and inevitably in such a rapidly changing field it already seems dated in parts. The standard of the contributions is mixed. Nevertheless, as a review of the subject with over 500 references it would be a useful acquisition for a urology departmental library.

J. W. H.

Book Received

Present Diagnosis and Treatment of Septicemia. (Antibiotics and Chemotherapy, Vol. 21)
Edited by L. P. GARROD and others. Basel: Karger, 1976. $48.25.

Conferences and Courses

10th International Congress of Chemotherapy

Zurich, 18th-23rd September, 1977

The programme will consist of symposia and free paper sessions in the field of antimicrobial and anticancer chemotherapy.

Official language: English.

For further information: Administrative Secretariat, 10th International Congress of Chemotherapy, P.O. Box 182, CH-4013 Basle, Switzerland.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The List of Current Urological Literature is now arranged to correspond to the order in which papers are published in the *Journal, i.e.* in anatomical order beginning with papers on the kidney.

A general section is included at the end.

KIDNEY

Congenital Anomalies. Partial hydronephrosis in a patient with horseshoe kidney and bilateral duplication of the pelvis and ureter. (J. Christoffersen and H.-G. Iversen.) *Scand. J. Urol. Nephrol.* 1976, **10**, 91.

Clinical and genetic aspects of the horseshoe kidney. (R. Meridies *et al.*) *Urol. Int.* 1976, **31**, 239.

Vascular supply of congenital high renal ectopia. (J. Wojtowicz and S. Zierhoffer.) *Fortschr. Geb. Roentgenstr Nuklearmed.* 1976, **124**, 355

Crossed renal ectopia: angiographic findings in six cases (Z. J. Rubenstein *et al*) *Am. J. Roentgenol.* 1976, **126**, 1035.

Crossed renal ectopia with colic: a clinical clue to embryogenesis. (D. G. Romans *et al.*) *Br. J. Urol.* 1976, **48**, 171.

Ectopic kidney. (A. M. Sanchez *et al.*) *Rev. Clin. Esp.* 1976, **141**, 293.

Rare variant of genital malformation with aplasia of right kidney. (M. Wunderlich.) *Zentralbl. Gynaekol.* 1976, **98**, 559.

Congenital mesoblastic nephroma. (P. Hermanek and A. Sigel.) *Fortschr. Med.* 1976, **94**, 1025.

Detection of renal anomalies by abdominal palpation in newborn infants (M. Perlman and J. Williams.) *Br. Med. J.* 1976, **2**, 347.

Maldeveloped kidney: its classification and time of onset. (H. Itatani *et al.*) *Jpn. J. Urol.* 1976, **67**, 178.

Congenital renal tract malformations: a comparison of two consecutive autopsy series during an eleven-year period. (H. McKenna.) *Med. J. Aust.* 1976, **1**, 519.

Malposition of colon in left renal agenesis and ectopia. (V. Mascatello and R. L. Lebowitz.) *Radiology*, 1976, **120**, 371

Trauma. Spontaneous rupture of allografted kidney. (G. Dostal *et al.*) *Langenbecks Arch. Chir.* 1976, **341**, 87.

Seat belt as cause of a severe isolated rupture of kidney. (R. Hartung and B. Egger.) *Unfallheilk. Traumatol.* 1976, **79**, 117.

Sub-adventitial traumatic rupture of the left renal artery. (C. Faure *et al.*) *J. Radiol. Electrol. Med. Nucl.* 1976, **57**, 291.

Rupture of left kidney following a renosplenic shunt. (R. J. Swanson *et al.*) *Surgery*, 1976, **79**, 710.

Spontaneous renal allograft rupture without rejection. (B. Anderson *et al.*) *J. Urol.* 1976, **115**, 745.

Spontaneous rupture of the kidney. (H. M. Nissen and N. G. Kjaer.) *Scand. J. Urol. Nephrol.* 1976, **10**, 173.

Association of renal injury with combined cephalothin-gentamicin therapy among patients severely ill with malignant disease. (J. E. Plager.) *Cancer*, 1976, **37**, 1937.

Urinary N-acetyl-beta-D-glucosaminidase as an indicator of renal damage in burned patients. (P. J. R. Boyd *et al.*) *Burns*, 1976, **2**, 76.

Complete avulsion of the renal pedicle due to blunt injury to abdomen. (D. G. Jenkins and K. G. Gupta.) *Br. J. Urol.* 1976, **48**, 12.

Histomorphologic features of ultrasonic renal injury. (A. Elbadawi *et al.*) *Arch. Pathol. Lab. Med.* 1976, **100**, 199.

Bilaterally small kidneys in shock. (R. W. Katzberg *et al.*) *J.A.M.A.* 1976, **235**, 2213.

Long term study of renal function in rabbits after unilateral kidney traumas. (A. E. Lison *et al.*) *Med. Welt*, 1976, **27**, 1336.

Long-term effects of warm ischemic injury on kidney. (A. S. Hermreck *et al.*) *Surg. Forum*, 1975, **26**, 323.

Intraperitoneal rupture of hydronephrotic kidney. (O. Ekwueme and S. A. Adibe.) *Br. J. Surg.* 1976, **63**, 637.

Infections. Renal abscess mimicking a Wilms' tumor. (D. A. Simonowitz and H. M Reyes.) *J. Pediatr. Surg.* 1976, **11**, 269.

Renal abscess: old problem with a new look. (E. B. Boone *et al.*) *Va. Med. Mon.* 1976, **103**, 483.

Prognosis of urologically induced pyelonephritis after surgical correction of urinary tract malformations. (E. Straub and K. Stockamp.) *Aktuel. Urol.* 1976, **7**, 65.

Pyelonephritis in patients with congenital malformations of urinary tract after corrective operation and under antibiotic therapy. (E. Straub and K. Stockamp.) *Monatsschr. Kinderheilk.* 1976, **124**, 511.

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Echinococcal disease of kidney. (H. M. Diamond *et al.*) *J. Urol.* 1976, **115**, 742.

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Nephroureterectomy in urinary tuberculosis. (Th. Burghele.) *Eur. Urol.* 1976, **2**, 1.

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Calcareous renal calculi: current medical treatment. (C. Y. C. Pal.) *Tex. Med.* 1976, **72**, 70.

Bilateral renal calculi in patients receiving methyldopa. (K. J. Murphy.) *Med. J. Aust.* 1976, **2**, 20.

Current surgical management of branched renal calculi. (R. A. Roth.) *Surg. Clin. North Am.* 1976, **56**, 753.

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[1] Titles in this list have been taken from those listed in *Current Contents: Clinical Practice* published by Institute for Scientific Information, Philadelphia.

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Duodenal and common bile duct obstruction with a pyelo-duodenal fistula caused by renal calculous pyonephrosis. (K. P. Boardman.) *Br. J. Urol.* 1976, **48**, 6.

Traumatic rupture as the presenting feature of a hydronephrosis with renal stones. (G. Violet and M. Robin.) *J. Urol. Nephrol.* 1976, **82**, 290.

Fasting urine excretion of magnesium, calcium and sodium in patients with renal calcium stones. (P. O. Schwille *et al.*) *Urol. Res.* 1976, **4**, 33.

Renal stones and coronary heart disease. (S. Ljunghall and H. Hedstrand.) *Acta Med. Scand.* 1976, **199**, 481.

Treatment of kidney stones from uric acids and urates. (G. Lagrue.) *Rev. Prat.* 1976, **26**, 1997.

Uric acid kidney stones. (D. Fritel.) *Rev. Med. (Paris)*, 1976, **17**, 809.

Natural history of nephrolithiasis. (Ph. Cassan *et al.*) *Rev. Med. (Paris)*, 1976, **17**, 797.

Calcium nephrolithiasis and idiopathic hypercalciuria in adults. (A. Baglin *et al.*) *Rev. Med. (Paris)*, 1976, **17**, 813.

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Primary aldosteronism and renal hypertension. (M. Vlaho *et al.*) *Med. Welt*, 1976, **27**, 1009.

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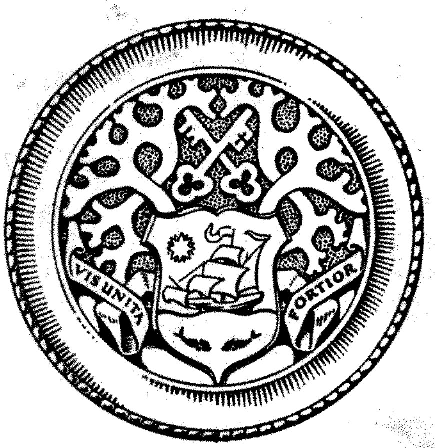

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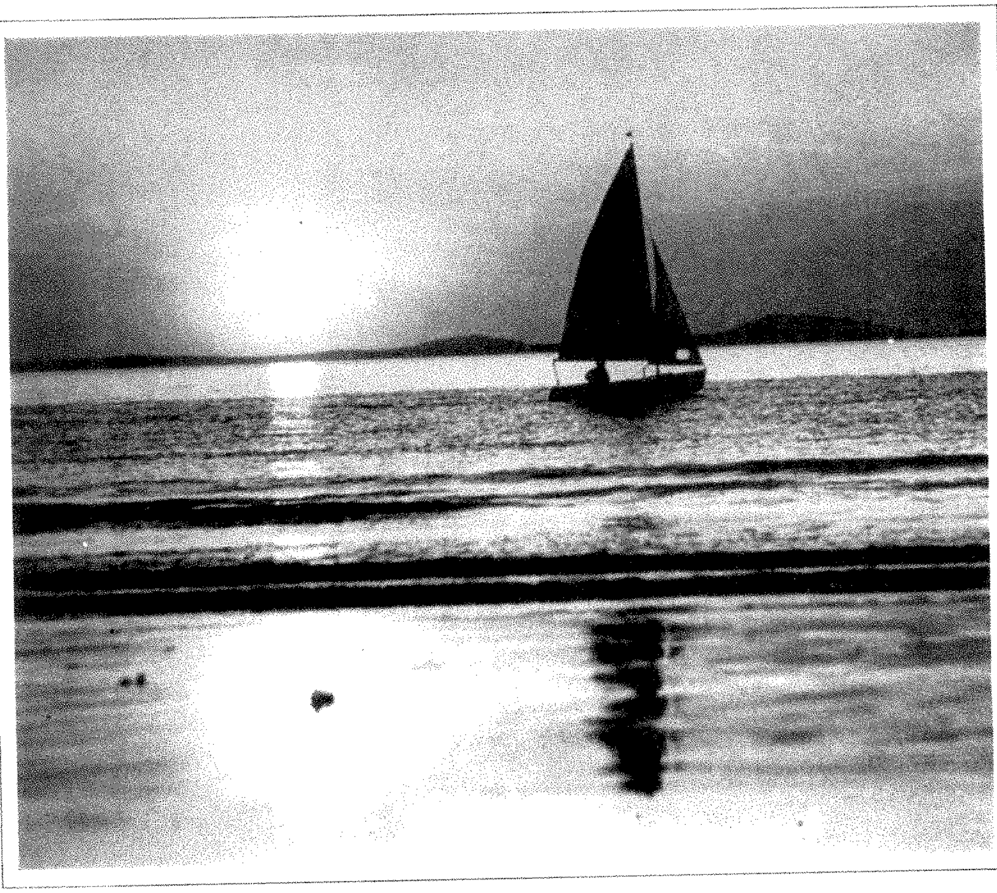

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Continued on page vi

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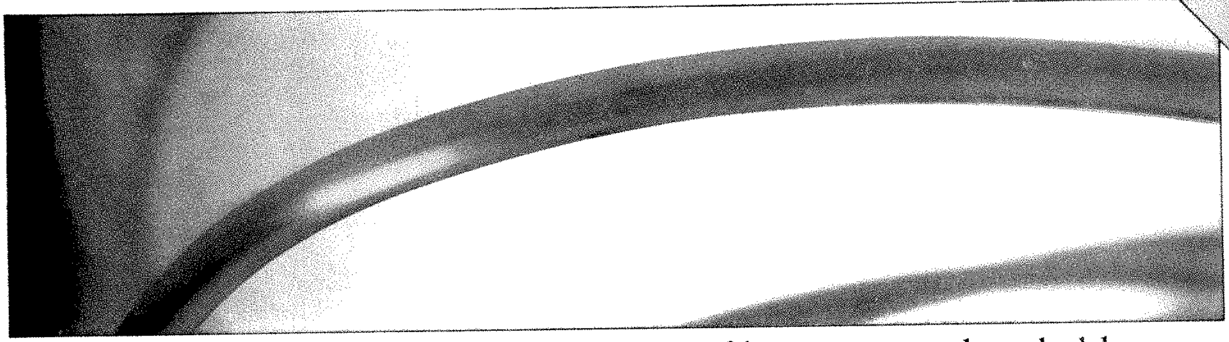

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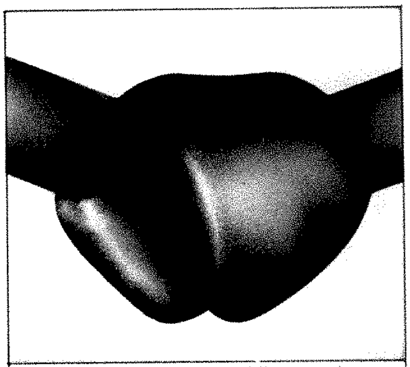

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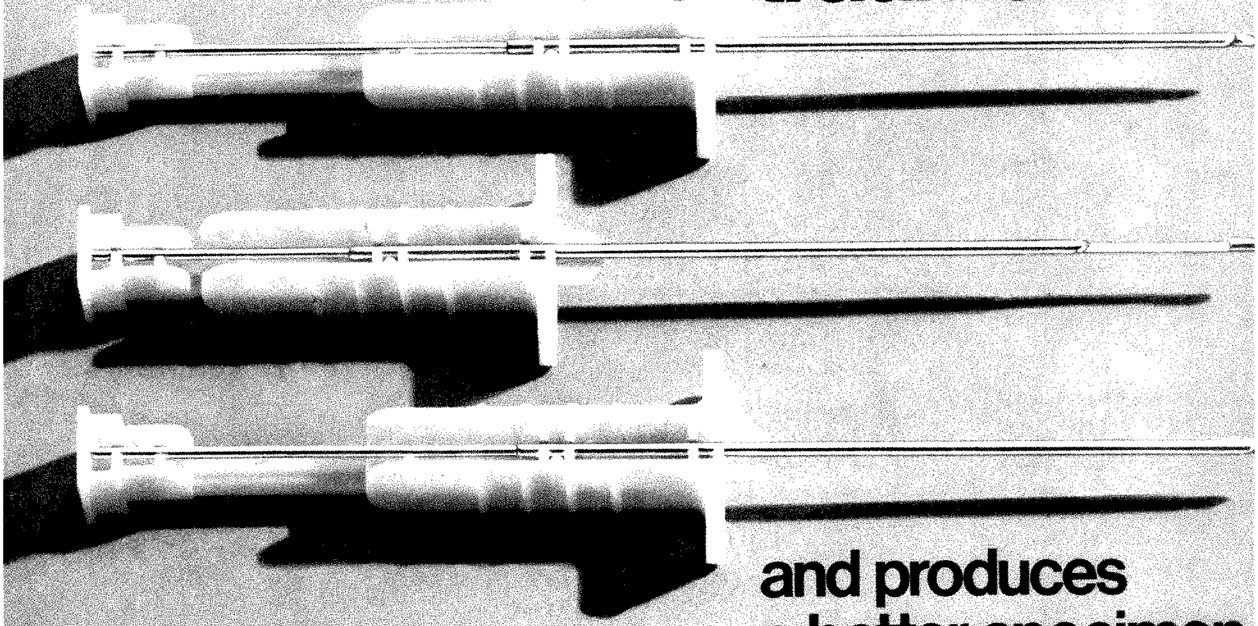

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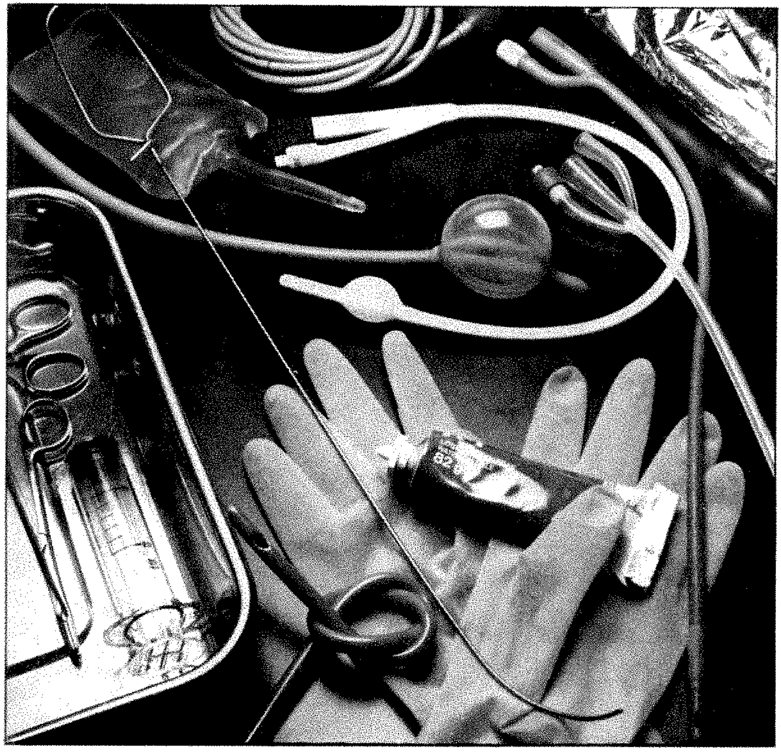

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Polycystic Renal Disease—Occurrence of Malignant Change and Role of Nephrectomy in Potential Transplant Recipients

R. J. REGAN, G. F. ABERCROMBIE and H. A. LEE

Wessex Regional Renal Unit, St Mary's Hospital, Portsmouth

(Received 20 August 1976; accepted for publication 15 September 1976)

The incidence of renal malignancies in patients with polycystic kidneys is unknown. With the longer duration of survival of patients with polycystic kidneys on dialysis and transplant programmes, who accounted for 8·0% of 25,302 patients in the registry of the European Dialysis and Transplant Association (Parsons *et al.*, 1974), and 5·4% of all renal diseases requiring transplantation (Twelfth Report of the Transplant Registry), it seems likely that the risk of developing such malignancies will increase.

This report presents details on 2 further patients with polycystic kidneys who developed renal neoplasms, 1 of whom was on regular haemodialysis treatment at the time. The association between polycystic kidneys and the development of malignant renal neoplasms is reviewed and the reasons for a management policy are discussed.

Case Reports

Of 147 patients treated in the Wessex Regional Renal Unit by regular haemodialysis between 1967 and 1976, 11 (7·5%) had polycystic kidneys. One of these developed a renal carcinoma (Case 1). Another patient developed a renal carcinoma before regular dialysis was started (Case 2).

Case 1. J. L. (born 1936)
This man was discovered to have polycystic disease of the kidneys following haematuria in 1958. His mother had died of renal failure, cause unknown, at 52 years of age. From 1966 onwards the patient experienced intermittent drawing pain in the right anterior abdomen. He also had occasional haematuria about every 2 years. His hypertension was controlled with methyl dopa. The two kidneys were approximately equal in size throughout, but the right kidney was often tender. Giovannetti diet was started in August 1972. In March 1973, following haemorrhage into the right kidney, regular haemodialysis became necessary. Both kidneys were grossly enlarged at that time. A right nephrectomy was performed in June 1973 because of continued right-sided pain and haematuria. Some of the cysts contained pus, as well as bloodstained fluid. There was no evidence of malignant change on histology.

An unsuccessful renal transplant was carried out in April 1974 and the kidney was removed in June 1974. Further haematuria occurred in September 1974. A second renal transplant was cancelled in May 1975 because of the enormous size of the left kidney. Elective nephrectomy was done later that month. The left kidney measured 35 × 21 × 15 cm and weighed over 5 kg. At operation a grossly abnormal para-aortic node was found and removed for histological examination. This showed metastatic clear cell carcinoma of the kidney. No tumour could be found on histological examination of the left kidney itself. The patient made a good recovery. Dialysis continues but no plans have been made for further transplantation.

Case 2 E. E. (born 1922)
This woman was known to have polycystic kidneys since 1947. Her mother died aged 48 from a cerebral haemorrhage related to hypertension secondary to her polycystic kidneys. The patient was first seen by one of us (HAL) in 1963. She had previously had bilateral Rovsing's operations. She suffered from recurrent attacks of haematuria, bilateral loin pain and urinary tract infection. On several occasions she developed salt wasting which required intravenous saline, during episodes of urinary tract infection.

At the time of her final illness in 1969 her serum creatinine had risen to 12·0 mg/100 ml and blood urea to 180 mg/100 ml whilst on a 30 g protein restricted diet. Her blood pressure was 160/80 and she had never required

Table I

Case	Authors	Sex	Age	Clinical features	Method of diagnosis	Pathology	Outcome
1-3	Walters and Braasch (1934)	M	67	?	?	Renal carcinoma	Died
		?	?	Two patients with "neoplasm of kidney"		?	?
		?	?			?	?
4	Tomoff (1937)	M	48	Haematuria, pain and mass in right loin	Cystoscopy—R. haematuria; retrograde—suggests tumour	Renal carcinoma	?
5	Van der Vuurst de Vries (1938)	M	58	Haematuria, weight loss, tired and giddy	Cystoscopy—L. haematuria; IVP—suggests L. tumour	Papillary carcinoma	Uraemia
6	Melicow and Gile (1940)	M	64	R. flank pain; frequency; haematuria; R. kidney larger than L.	IVP—mass in R. kidney	Renal carcinoma	Metastases
7	Fey and Busser (1941)	M	63	Mass in L. flank	IVP—L. tumour nephrectomy	Renal carcinoma	Died post-op.
8-9	Clemmesen (1942)	M	52	Haematuria; bilateral masses ascites; hepatomegaly	–	? renal carcinoma	Died
		M	38	Haematuria; fever	R. nephrectomy	Renal carcinoma	Died; metastases at autopsy
10	Bobbitt (1943)	M	46	Pain R. side and back; haematuria	Cystoscopy—R. haematuria; exploration R. kidney	Renal carcinoma	Metastases
11-12	Lowsley and Curtis (1945)	?	?	?	On post-mortem sections	Angiomyosarcoma	Died
		F	?	?	Nephrectomy	Fibrosarcoma	?
13	Baurys (1945)	M	75	Haematuria, L. flank pain	Exploration	Renal carcinoma	Recovered
14	Hayward (1946)*	F	72	Mass in L. abdomen; haematuria	Cystoscopy—L. haematuria; exploration L. kidney	Renal carcinoma	Metastases
15	Baurys and Morton (1950)*	M	76	Pain and mass in L. flank	IVP—non-functioning L. kidney; L. nephrectomy	Papillary carcinoma	Recovered
16	Tallarigo (1950)	M	63	Haematuria pain and mass in L.	Laparotomy for duodenal ulcer	Renal carcinoma	Well at 2 years
17	Lewis and Kimbrough (1952) Borski and Kimbrough (1954)	M	38	Headaches; R. kidney larger than L.	Exploration R. kidney	Renal carcinoma	
				3 years later—L. kidney increased in size	L. Rovsing's operation and biopsy	Renal carcinoma	Died 2 years later with metastases
18	Johnson (1953)*	M	58	Claudication in legs; mild hypertension	IVP—calyceal distortion on L; L. nephrectomy	Malignant papillary cystadenoma	Well at 2 years

19	Puigvert (1958)	F	26	Haematuria; L. lumbar pain; L. kidney larger than R.	Cystoscopy—L. haematuria; IVP—non-functioning L. kidney. L. nephrectomy for anaemia due to bleeding	Papillary carcinoma	
				Later R.-sided pain; R. kidney increased in size	Exploration; R. lower pole nephrectomy	Undifferentiated epithelial tumour	Well 3 years later
20	Brannan, Miller and Crisler (1962)	F	65	Fever; L. loin pain; large L. lower pole mass	Exploration	Renal carcinoma	Died
21	Howard and Young (1969)	F	32	L. abdominal mass	IVP—mass L. kidney. Arteriogram—2 tumours	2 renal carcinomas	Recovered
22	Siegelman, Zavod and Hecht (1971)	M	54	(Neurofibromatosis) low back pain	IVP—non-lucent mass, lower R. kidney; arteriogram—tumour R. cystoscopy—R. haematuria	Renal carcinoma	Recovered
23	McFarland, Wallace and Johnson (1972)	F	45	Pathological fracture clavicle; palpable L. kidney	IVP—rounded L. upper pole; arteriogram—tumour	Renal carcinoma	Recovered
24	Ahmann, Wurster and Ceccarelli (1973)	M	63	Gross painless haematuria	IVP—suspicious on L. side. Arteriogram—suspicion of tumour	Transitional cell carcinoma (of renal pelvis)	Recovered
25	Cole and Gill (1973)	M	71	Hypertension; haematuria; R. femoral hernia and obstructed R. ureter	IVP—non-functioning R. kidney. Arteriogram—no tumour seen. Retrograde pyelogram—possibility of tumour	2 renal carcinomas	Recovered
26	Posso, Safadi and Van Dyk (1973)	M	20	Weight loss; diarrhoea; calcified mass R. upper abdomen	IVP—showed the mass to be in the R. kidney; laparotomy	Renal carcinoma	Recovered
27	Roberts (1973)	M	44	R. kidney larger than L., fixed lower pole. Nodules in chest X-ray; calcification both renal areas	Arteriogram—tumour on R. side. Autopsy—bilateral tumours	Bilateral renal carcinomas	Died
28	Wright *et al.* (1974)	F	19	Haematuria, progressive renal failure	Cystoscopy—L. haematuria; nephrectomy for bleeding	Angiomyolipo-sarcoma	Required dialysis 9 months later

* Unilateral polycystic kidney.

antihypertensive drugs. She developed anorexia, nausea, vomiting and weight loss out of proportion to her chronic renal failure. Both kidneys had increased in size over the years but the right kidney was considerably larger than the left. Her haemoglobin was 9·4 g/100 ml and she had a leuco-erythroblastic anaemia. Barium meal was normal but a plain abdominal X-ray showed calcification over the right kidney which had not been present 2 years earlier. She died in July 1969.

At autopsy both kidneys showed typical polycystic changes. In the right kidney there was a dense, circular infiltrating mass with a necrotic centre containing small plaques of calcification. There were multiple nodular metastases in the liver. Histological examination revealed a renal carcinoma.

Review of Cases from the Literature

28 patients with renal malignancies occurring in polycystic kidneys have previously been described (Table I). There were 18 males, 7 females and 3 whose sex was not recorded. Of 24 patients whose ages are known the mean age was 52·4 years (19-76). Histological diagnoses were recorded for 25 patients and are shown in Table II. The tumours were mainly epithelial in origin (carcinomata) but some were mesenchymal (sarcomata). None of these cases occurred in patients on regular dialysis or with renal transplants, so that our Case 1 is the first such report.

The commonest presenting features in the 28 cases in decreasing order of frequency were: haematuria (13), abdominal or flank pain (9), unilateral mass (8), unequal enlargement of the kidneys (4), features suggestive of metastases, *e.g.* pathological fracture (4) and renal calcification (2). The diagnosis of renal malignancy was confirmed or suggested by intravenous pyelography or retrograde pyelography in 10 cases and by arteriography in a further 5 cases. However, in at least 13 cases diagnostic certainty was only achieved by exploration of the kidney. Thus there was no uniform, well-defined clinical-investigatory diagnostic combination.

Discussion

In the published reports of malignancies in polycystic kidneys the definitive diagnosis has relied on renal arteriography or renal exploration carried out because of a symptom or combination of symptoms in patients without grossly impaired renal function. In some cases the finding of a tumour was incidental, as in our Case 1, when nephrectomy was undertaken because of gross renal size. The occurrence of a unilateral renal mass with or without loin pain or haematuria, or one of these findings accompanied by renal calcification or evidence of metastases suggests renal malignancy. Excretion urography, renal arteriography and renal exploration may be carried out as appropriate.

Several difficulties arise in applying these methods to patients with polycystic kidneys already being treated by regular dialysis. Haematuria is not uncommon in these patients, particularly since they are intermittently heparinised during dialysis. Abdominal pain or loin pain also occurs not infrequently and may be due to haemorrhage into a cyst or to urinary tract infection. Unequal enlargement of the polycystic kidneys is also not a rare finding in non-malignant cases. The symptoms are therefore non-specific and indicate the need for further investigation if the diagnosis of malignancy is to be confirmed or refuted other than by awaiting evidence of metastases.

Renal calcification remains a valid sign but is not seen commonly enough for plain abdominal X-ray to be of significant value as a routine screening aid. The more specialised diagnostic techniques are less applicable to patients with virtually no renal function and non-specific symptoms. Excretion urography is of no value in demonstrating renal morphology in these patients. Renal arteriography could theoretically be helpful in making the diagnosis but raises the question of when and how often it should and could be done. Repeated use of invasive techniques such as arteriography as a routine screening procedure cannot be justified and even if it were reserved for symptomatic polycystic patients repeated examinations would accumulate. None of the currently available diagnostic methods is sufficiently reliable and safe to be used repeatedly as a

Table II

Histological Diagnosis of Malignant Renal Neoplasms in Polycystic Kidneys

Histology	Number of cases
Renal carcinoma (hypernephroma) (adenocarcinoma)	17
Papillary carcinoma, cystadenoma and "undifferentiated epithelial tumour" and transitional cell carcinoma	5
Angiomyosarcoma, fibrosarcoma and angiomyolipo-sarcoma	3
Unknown or not stated	3
Total	28

routine screening procedure for renal malignancy in patients on regular haemodialysis for polycystic kidneys. Therefore, bilateral nephrectomy must be considered for these patients.

Although the incidence of malignant change in polycystic kidney disease is unknown it has been regarded as a premalignant state (Tallarigo, 1950). The occurrence of malignancy is not confined to either sex and no age group is exempt. Several factors may contribute to an increased risk in regularly dialysed or transplanted patients: (1) increased duration of survival in the pre-malignant state, (2) increased duration of uraemia which may lead to partial immunosuppression and increased likelihood of malignancy (Tasker *et al.*, 1975) and (3) the effect of immunosuppressive therapy following renal transplantation (Penn and Starzl, 1972). These workers reported a considerably increased risk of developing both epithelial and mesenchymal malignancies in patients on immunosuppressive therapy. They included many cases of renal malignancies but none were in polycystic kidneys. However, it is likely that polycystic kidneys are equally or perhaps more susceptible to the oncogenic effects of immunosuppression.

Apart from Roberts (1973), who raised the question of prophylactic bilateral nephrectomies for patients with polycystic kidneys on dialysis and transplant programmes because of the risk of malignancy, there have been no other advocates of this course of action. Although Amamoo, Woods and Anderson (1974) recommended routine removal of polycystic kidneys before transplantation their reasons were poorly defined. Usually a desire to preserve potentially beneficial renal tissue and to avoid the surgical risks of bilateral nephrectomy has prevailed (Salvatierra, Kountz and Belzer, 1973; Freed, 1976; Salvatierra *et al.*, 1976). The last-named authors recommend bilateral nephrectomies in selected cases of polycystic kidneys for renal infection (approximately 30% of the patients), haematuria or very large kidneys which may make transplantation difficult or impossible (cf. Case 1).

The principal disadvantage of rendering these patients anephric is loss of erythropoietin which invariably produces more severe anaemia (Ypersele de Strihou and Stragier, 1969). Various measures are, however, available for treating the anaemia if necessary, such as oral cobalt chloride therapy (Duckham and Lee, 1976). Although bilateral nephrectomy may impose further fluid intake restrictions upon these patients, since some may still have appreciable urine volumes even when on regular dialysis treatment, this has not been a serious problem in our patients.

In our view the risk of developing malignancy should be regarded as an added indication for bilateral nephrectomy in patients with polycystic kidneys awaiting renal transplantation. This consideration would weigh in favour of such operation on all those patients with symptoms referable to their polycystic kidneys since all but 1 of the patients with malignant change in polycystic kidneys collected from the literature had renal symptoms. It remains advantageous to preserve the kidneys of totally asymptomatic patients whose polycystic kidneys are not grossly enlarged. Even so, it may be advisable to reconsider removing the polycystic kidneys after renal transplantation when their residual erythropoietic and other functions have been assumed by the transplanted kidney, since at this stage the risk of malignant change may be greater.

Summary

28 cases of malignant renal neoplasms in patients with polycystic kidneys are reviewed from the literature and 2 new cases are reported.

The difficulty in diagnosing this malignant change together with the increased survival of patients with polycystic kidneys on dialysis and transplant programmes leads to the recommendation that all such patients should be considered for nephrectomies. The reasons for this recommendation and its advantages and disadvantages are discussed.

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The Authors

R. J. Regan, MRCP, Senior Registrar in Nephrology.
G. F. Abercrombie, FRCS, Consultant Urologist, Department of Urology, St Mary's Hospital.
H. A. Lee, FRCP, Professor of Metabolic Medicine.

Requests for reprints to Dr R. J. Regan, Wessex Regional Renal Unit, St Mary's Hospital, Portsmouth.

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Short Case Report

Retroperitoneal Liposarcoma

Case Report

A man aged 80 was admitted with a history of aching in the back and in the left iliac fossa for two months. He was not aware of a large lump in the left lumbar region but knew of a varicocele in his left scrotum since December 1974. There was a very large fixed mass in his left lumbar region which could not be distinguished from the left kidney and did not appear to be related to the colon. IVU showed a soft tissue shadow in the left lumbar region pushing the colon forwards, displacing the renal pelvis and ureter medially, and compressing the lower calyces (Fig.).

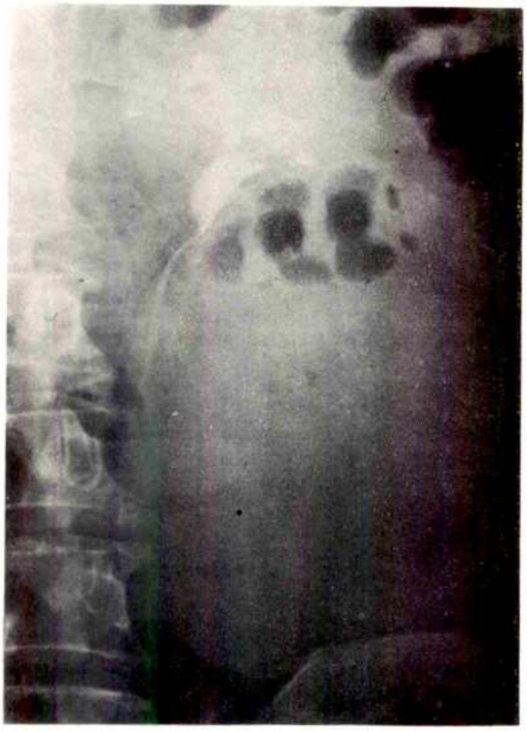

Fig. Intravenous urogram taken in March 1975.

The left kidney was explored through the bed of the 12th rib, but surprisingly the tumour mass proved to be perinephric, lying over the lower pole of kidney, ureter, and testicular vessels and was friable and necrotic in places. It was mobilised and removed in one piece without damaging the ureter and testicular vessels. The tumour weighed about 2,000 grams and looked like a brain. Histologically it was pleomorphic liposarcoma.

The varicocele disappeared in 2 weeks but he died of recurrence at home 8 months later.

Comments

This tumour, representing 13·3% of all liposarcomata (Spittle *et al.*, 1970), is very rare at this age. The associated left-sided varicocele, which has never been reported before in the literature, added to the diagnostic dilemma. The prognosis depends more upon complete excision rather than on incomplete surgery combined with radiotherapy. Local recurrence is common irrespective of treatment and distant metastases are rare (Kinne *et al.*, 1973).

I wish to thank Mr A. F. Robinson, Consultant Surgeon, Burnley Group Hospitals, for his permission to report this case.

S. K. Saha[1]

[1] Present address: Montagu Hospital, Mexborough, Rotherham.

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Late Ureteric Obstruction in Renal Transplantation

MARTIN G. MCLOUGHLIN

Department of Urology, The James Buchanan Brady Urological Institute,
The Johns Hopkins Hospital, Baltimore, Maryland 21205

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Improved survival in patients undergoing renal allotransplantation has resulted in a patient population that is now producing late obstruction to the drainage system (Martin *et al.*, 1969). The need to recognise this clinical entity early in its development may improve the graft survival rate. Review of our transplant patients revealed 5 cases of ureteric obstruction occurring later than 3 years after renal allotransplantation.

Patients

Review of 305 renal transplants performed at The Johns Hopkins Hospital and Baltimore City Hospitals since 1968 produced 5 cases of late ureteric obstruction. There were 4 cases of ureterovesical junction stenosis and only 1 case of ureteropelvic junction obstruction. Intravenous urograms were ordered in these 5 patients because of changes in renal function and because 2 patients were also being evaluated for persistent urinary tract infections. 4 out of the 5 patients had undergone a surgical exploration in the immediate post-transplant period: 1 for bleeding, 2 for extravasation and 1 patient for perinephric fluid collection. The case histories will be presented.

Cases

A 39-year-old female received a cadaveric renal allograft that functioned well for 3 years. In the early postoperative period she required exploration of the wound for haemorrhage. This was successfully controlled and the renal graft functioned to result in a serum creatinine of 1·2 mg per 100 ml. Intravenous pyelogram at 2½ years showed a ureterovesical junction obstruction with proximal dilatation but this was followed conservatively since her serum creatinine was stable. A rise in her serum creatinine to a level of 10 mg per 100 ml, proteinuria and weight gain, necessitated ureterovesical junction exploration. A transvesical ureteral orifice meatotomy with ureteral splint placement was performed as definitive therapy. In the postoperative period she displayed no post-obstruction diuresis and her creatinine never fell below a level of 9·6 mg per 100 ml. She subsequently had a progressive rise in serum creatinine, infection and sepsis necessitating a transplant nephrectomy and return to chronic dialysis.

A 35-year-old female's past history revealed bilateral ureteric reflux that resulted in end-stage pyelonephritic kidneys. Prior to receiving her transplant, bilateral nephro-ureterectomies were performed to remove the chronically infected kidneys. She received a cadaveric renal allograft that functioned well. In the postoperative period she was explored because of fever and had a perinephric fluid collection drained successfully. 3 years after the successful implantation she presented with severe pain over the graft. Her serum creatinine had acutely risen from 1·2 mg to 2·2 mg per 100 ml and intravenous urogram showed ureterovesical obstruction. She was explored and the stenotic segment resected. The shortened ureter was then reimplanted into the area of the bladder fixed by a psoas hitch and splinted internally with a number 8 feeding tube. Her postoperative course was uneventful and she was discharged with a serum creatinine of 1·5 mg per 100 ml.

A 35-year-old male had a second renal allotransplant which functioned normally for 3 years. At that time, urinalysis showed bacteria and repeated urine cultures were positive for *Serratia marcescens* and *Proteus mirabilis* An IVP showed marked ureteric obstruction. At operation the area around the renal hilus was severely scarred, and what was thought to be the renal pelvis was opened and straw-coloured fluid emerged. To be certain that this was the renal pelvis the cavity was injected with renografin, but the study did not reveal calyceal structures.

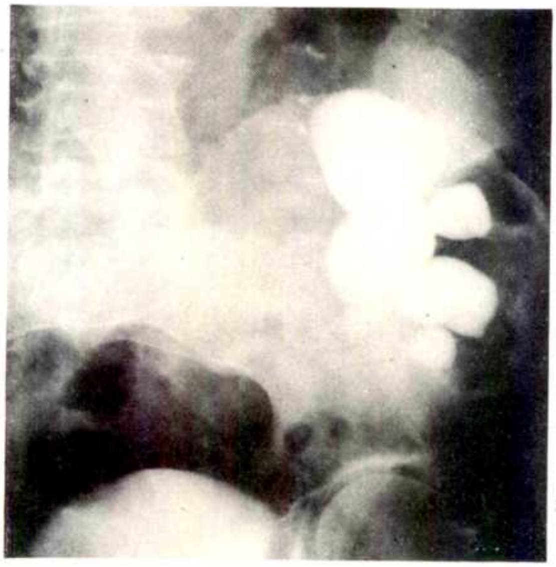

Fig. Intravenous urogram demonstrating a hydronephrosis with a suggestion of blockage at the ureteropelvic junction.

We then identified the renal pelvis in close proximity to this tense cyst and performed a ureteric-pyelostomy. Patency of this anastomosis was confirmed radiographically and no leaks were found by injecting sterile milk into a ureteric catheter. The incision was closed and convalescence was uneventful.

A 26-year-old female underwent bilateral nephrectomy for chronic glomerulonephritis and subsequently received a kidney from her father in March 1969. In the early postoperative period she was re-explored because of a urinary fistula and this was successfully closed. In March 1975 because of recurrent urinary tract infection and demonstrated obstruction at the ureterovesical junction she underwent a ureteropyelostomy utilising the recipient ureter to the transplant renal pelvis. 10 days postoperatively she developed a urinary fistula from a partially separated ureteropyelostomy anastomosis. This disruption was successfully closed and a postoperative course was uneventful with a serum creatinine of 1·5 mg per 100 ml on discharge from hospital.

A 56-year-old male developed chronic renal failure secondary to chronic glomerulonephritis. In May 1973, a kidney donated by his brother was placed in his left renal fossa. Because of a short ureter the usual ureteroneocystotomy could not be done and ureteropyelostomy utilising his own ureter to the donor pelvis was performed using running 6·0 Prolene suture. 5 days after the transplant he was explored because of a large pyelocutaneous fistula. The disrupted ureteropyelostomy was closed with a 6·0 Prolene suture. Postoperatively, he did very well and was discharged from hospital 7 days after the cutaneous fistula. He was seen in March 1976; there were red cells in his urine, mild hypertension with diastolic values of 100 mm Hg and a serum creatinine of 1·5 mg per 100 ml. An intravenous urogram showed ureteropelvic junction obstruction (Fig.) and this was confirmed by a retrograde pyelogram. He was explored transabdominally and after reflecting the left colon, the ureter was found and traced to the ureteropelvic junction. Dense scar tissue was noted around the ureteropelvic junction. On opening the ureteropelvic junction, a 1 cm stone attached to a Prolene suture was removed. Analysis of this stone was calcium oxalate phosphate. A #8 feeding tube was placed down the ureter and into his bladder and utilised as an internal splint. Any attempt to close the pyelotomy would have resulted in stenosis. Mobilisation could not be performed to perform a pyeloplasty. An incision was made in the capsule and a rotational capsular flap was performed suturing the capsule over the pyelotomy with interrupted 4-0 Dexon sutures. Postoperatively, he developed ileus and on the 7th day postoperatively he had a subendocardial infarct with an uneventful recovery. On the 14th day postoperatively, the internal splint was removed and an intravenous pyelogram showed prompt function with no delay. His serum creatinine is 1·0 mg per 100 ml. He is no longer hypertensive and has been discharged from hospital.

Results

Surgical correction of these cases was varied and resulted in 4 out of the 5 grafts being salvaged. The 1 failure resulted from the transvesical ureteric meatotomy with ureteric splinting. Local infection and sepsis necessitated a transplant nephrectomy to ensure patient survival. One patient with ureterovesical junction obstruction had a successful ureteric neocystotomy to provide urinary drainage. This surgical procedure was necessary since the preferred technique of utilising the recipient's ureter and donor renal pelvis to perform a splinted ureteric pelvic junction anastomosis could not be done since the recipient ureter had been totally removed during nephrectomy because of massive ureterovesical reflux. 2 patients had ureteropyelostomy with the recipient ureter to the donor pelvis with good results. The ureteropelvic junction reconstruction was performed with an internal splint and was left free in the bladder. This 8F feeding tube was subsequently removed endoscopically. The 5th patient, who presented with ureteropelvic junction obstruction with a 1 cm stone, was successfully treated with a rotation capsular flap after removal of the stone. This procedure ensured a patent anastomosis with a watertight closure.

Discussion

Late ureteric complications need to be recognised during the early phase of their development so that irreversible renal damage does not result in graft loss. The follow-up of renal allotransplant recipients should include intravenous urography at least every 3 months in the early period and at least every 6 months for the duration of the graft survival. The pathophysiology of why ureteropelvic junction obstruction occurs at such a late date needs more clarification. The supposition that rejection of the ureter may have played a role seems inappropriate since once the obstruction was relieved in 4 out of the 5 cases, the renal function did return to normal without any active treatment of the rejection process. The fact that 4 out of the 5 cases did have re-exploration of the renal transplant early in the postoperative period after the initial implantation may be significant. This could be responsible for the late fibrosis and subsequent decreased vascular supply to produce ischaemic changes with resultant stenosis of the lower ureter and ureterovesical junction.

The patient with the stone and ureteropelvic junction fibrosis had obvious stenosis secondary to fibrosis. This stasis producing stenotic area plus the presence of the foreign body suture resulted in the calculus formation.

A rational surgical approach needs varied techniques as evidenced by this series. The use of transvesical meatotomy resulted in the only failure. The possible explanation being that poor blood supply to the ureterovesical junction in these stenotic lesions does not lend itself to a local surgical manoeuvre. The subsequent leakage and infection resulted in the need for a transplant nephrectomy.

The ureteroneocystotomy performed required that we sacrifice a lower part of the ureter and do a modified psoas hitch procedure to stabilise the bladder segment that the ureter was implanted into (Williams *et al.*, 1970). This bypassed any question of vascular supply to the lower ureter and ensured that the placement of this shortened ureter would be performed without tension into a fixed bladder location.

The technique of choice seems to be one in which the recipient's ureter and donor pelvis can be utilised with internal splinting of the ureteropelvic junction reconstruction. The need for nephrostomy drainage (Presto, Middleton and Bateman, 1973), 2-stage procedures or the need to use splints that are brought through the bladder or kidney did not seem necessary in our small series. These standard urological diversion devices are used in our cases where extravasation is the primary problem. In one patient the renal capsule was used as a rotational flap for adequate closure of the ureteropelvic junction defect without subsequent stenosis; an internal splint provided adequate diversion during the healing phase.

Conclusion

These 4 cases of ureterovesical junction obstruction and 1 case of ureteropelvic junction obstruction in patients who had received a transplant more than 3 years prior to presentation show a varied number of the causes of obstruction.

The need to assess each case on its merits and use the surgical technique appropriate has been reviewed.

The use of ureteric meatotomy alone provided the only failure in this series.

The recommended approach is to anastomose the recipient's ureter to the donor pelvis and to splint the ureteropelvic junction reconstruction.

If this defunctioned ureter is not available as in 2 cases presented, then a psoas hitch with a ureteroneocystotomy or rotation capsular flap may provide adequate drainage with favourable results.

Summary

5 cases of ureteric obstruction occurring in renal allotransplant recipients who had received their grafts more than 3 years prior to presentation are reviewed.

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The Authors

Martin G. McLoughlin MD, Assistant Professor of Urology.

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The Interrelationship between Vesico-ureteric Reflux, Trigonal Abnormalities and a Bifid Pelvicalyceal Collecting System: a Family Study

J. D. ATWELL, P. L. COOK, LESLEY STRONG and I. HYDE

Wessex Regional Centre for Paediatric Surgery, Southampton General Hospital, Tremona Road, Southampton

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Two previous family surveys of the parents and siblings of infants and children with bifid or double ureters have supported the hypothesis that the inheritance of a duplex urinary tract is by an autosomal dominant gene of variable penetrance (Whitaker and Danks, 1966, Atwell *et al.*, 1974). In the second of these investigations siblings were found with vesico-ureteric reflux unassociated with a duplex urinary tract; this occurred in 3 of the 30 families investigated; 2 of the 3 had pyelonephritic scarring. The association of vesico-ureteric reflux to the lower pole of the kidney in patients with double ureters is well known (Williams, 1968) as is also the

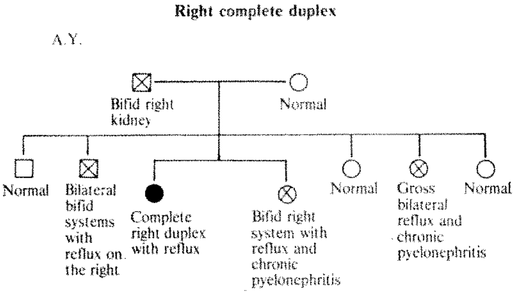

Right complete duplex
A.Y.
Bifid right kidney
Normal
Normal
Bilateral bifid systems with reflux on the right
Complete right duplex with reflux
Bifid right system with reflux and chronic pyelonephritis
Normal
Gross bilateral reflux and chronic pyelonephritis
Normal

Fig. 1a

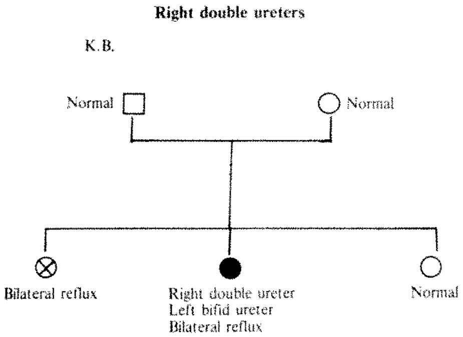


Fig. 1b

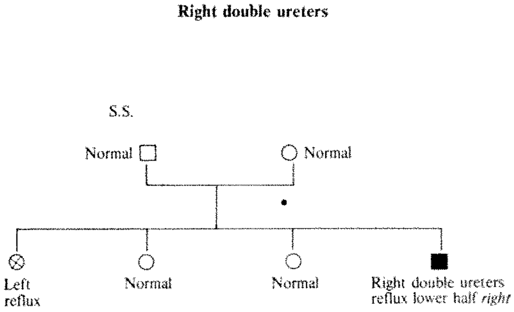


Fig. 1c

Fig. 1a-c Family trees of the original 30 families investigated to determine the familial incidence of bifid and double ureters. Note the three siblings with vesico-ureteric reflux unassociated with a duplex urinary tract.

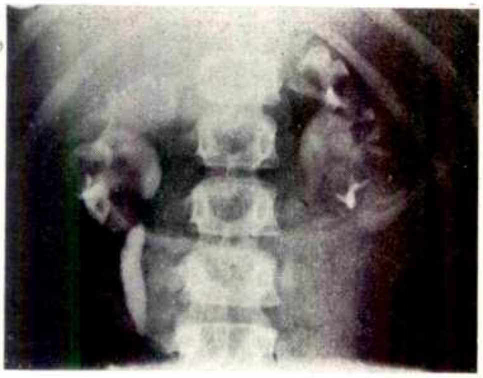
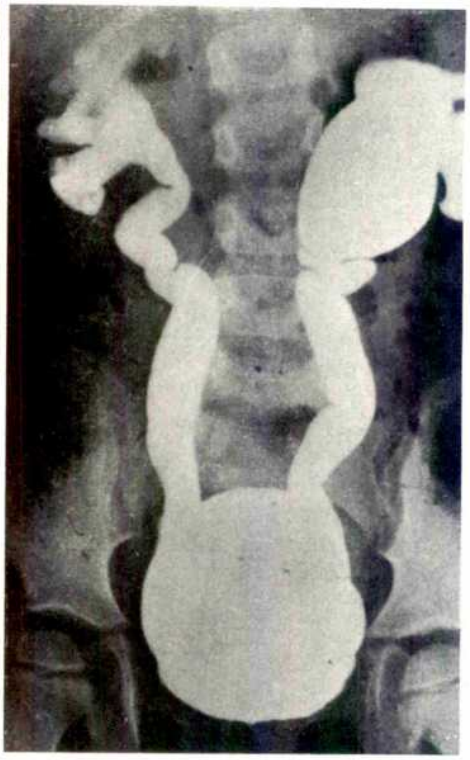


Fig. 2a



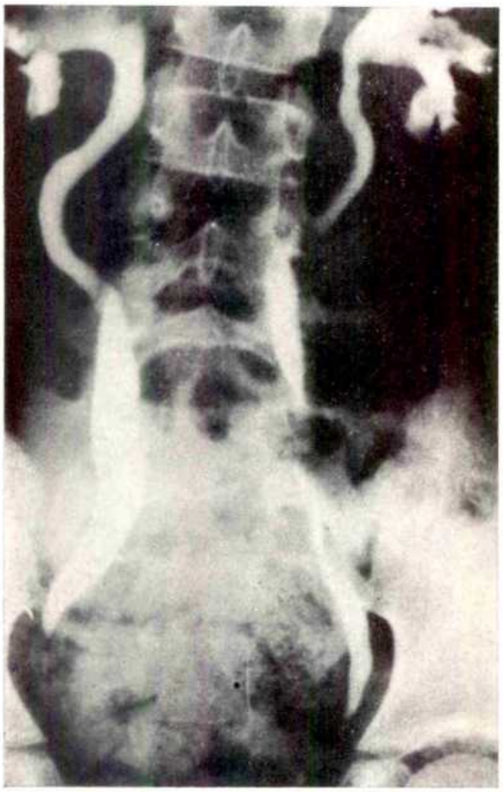


Fig. 2b

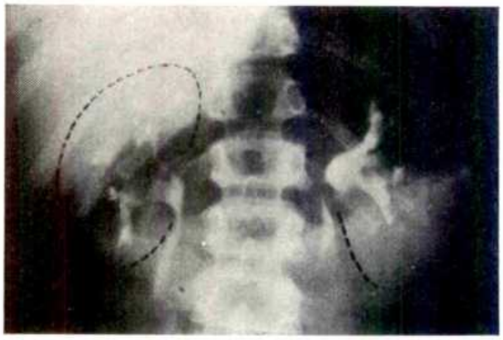


Fig. 2a and b. Chronic pyelonephritis and bilateral reflux in siblings for the families shown in Fig. 1a and 1b.

association of trigonal abnormalities with vesico-ureteric reflux (Lyon, Marshall and Tanagho, 1969). However, the association of idiopathic vesico-ureteric reflux and the other forms of duplicity of the urinary tract such as bifid renal pelves and ureters is more obscure. The purpose of the following investigations has been to study the interrelationship between vesico-ureteric reflux, trigonal abnormalities and a bifid pelvicalyceal collecting system and to suggest that genetic factors are important in the causation of idiopathic primary reflux.

Investigations and Methods

(i) *Association of Reflux in Siblings of Patients with a Duplex Urinary Tract*

The 3 families outlined in the introduction are included as a separate subgroup.

(ii) *Association of Reflux with a Bifid Pelvicalyceal System*

Between 1969 and 1975 116 patients were investigated for evaluation of a duplex urinary tract by intravenous pyelography, micturating cystography (110 patients), cystoscopy and retrograde ureterography as required. All of these children had presented with recurrent urinary tract infections.

(iii) *Incidence of a Bifid Pelvicalyceal Collecting System in Parents and Siblings of Index Patients with "Idiopathic Vesico-ureteric Reflux"*

There were 32 index patients with idiopathic reflux (male 9, female 23). The first-degree relatives (parents and siblings) were investigated by limited intravenous pyelography using a control and a 20-min film. In some patients in whom abnormal pyelograms were found further investigations such as cystoscopy and micturating cystography were carried out. Duplicity of the pelvicalyceal system was either unilateral or bilateral and defined as (i) a bifid renal pelvis, (ii) a bifid ureter, (iii) double ureters. Types (i) and (ii) were classified as an incomplete duplex system and type (iii) as a complete duplex system.

Results

(i) *Association of Reflux in Siblings of Patients with a Duplex Urinary Tract*

This association was found in 3 of the original 30 families investigated to determine the familial incidence of bifid and double ureters (Atwell *et al.*, 1974). The family trees of these are shown in Figures 1A-C. Chronic pyelonephritis was found in 2 of these siblings without evidence of duplicity of the pelvicalyceal system (Fig. 2a and b).

(ii) *Association of Reflux with a Bifid Pelvicalyceal System*

In the series of 116 patients, 110 had a micturating cystogram. Vesico-ureteric reflux was found in

Table I

Incidence of Reflux to the Ipsilateral and Contralateral Kidneys in Patients with Complete and Incomplete Duplicity of the Upper Urinary Tract

	116 patients (6 no cystogram)		
	Reflux	Ipsilateral	Contralateral
Double ureters	40	33	7
Bifid ureters	12	9	3
Bifid pelvis	10	6	4
Total	62	48	14

Table II

Radiological Findings in the First-degree Relatives (Parents and Siblings) of Index Patients with Idiopathic Vesico-ureteric Reflux

	Radiological findings		
Relationship to index patient	Bifid pelvicalyceal system	Bifid or double ureters	Lateral ectopia: reflux
23 fathers	3	1	–
23 mothers	2	–	–
54 siblings	3	2	8
100 relatives	8	3	8

Table III

Radiological Findings in the Siblings of the 9 Male and 23 Female Index Patients with Idiopathic Vesico-ureteric Reflux

	Radiological findings		
	Bifid pelvicalyceal system	Bifid or double ureters	Lateral ectopia: reflux
15 siblings of 9 male index patients	1	1	1
39 siblings of 23 female index patients	2	1	7

Table IV

Radiological Findings in Siblings in 9 Families with 1 Parent affected and in 13 Families with Neither Parent affected

9 families: 1 parent affected
17 of 26 siblings affected

13 families: neither parent affected
17 of 35 siblings affected

62 patients (56%). The reflux was to the ipsilateral kidney in 48 patients (77%) and to the contralateral kidney, unaffected by duplicity, in 14 (23%). This finding of reflux to the contralateral kidney in patients with a unilateral duplication was fairly common whether the duplication was complete or incomplete (Table I).

(iii) *Incidence of a Bifid Pelvicalyceal Collecting System in Parents and Siblings of Index Patients with "Idiopathic Vesico-ureteric Reflux"*

In the 32 families investigated there were 122 first-degree relatives (64 parents, 58 siblings). It was only possible to perform limited intravenous pyelography in 23 fathers and 23 mothers and in 54 of the 58 siblings—thus 100 (82%) of 122 possible relatives were investigated.

The radiological findings in these relatives are shown in Table II. This shows that in 19 first-degree relatives there was either a bifid pelvicalyceal collecting system or lateral ectopia of the

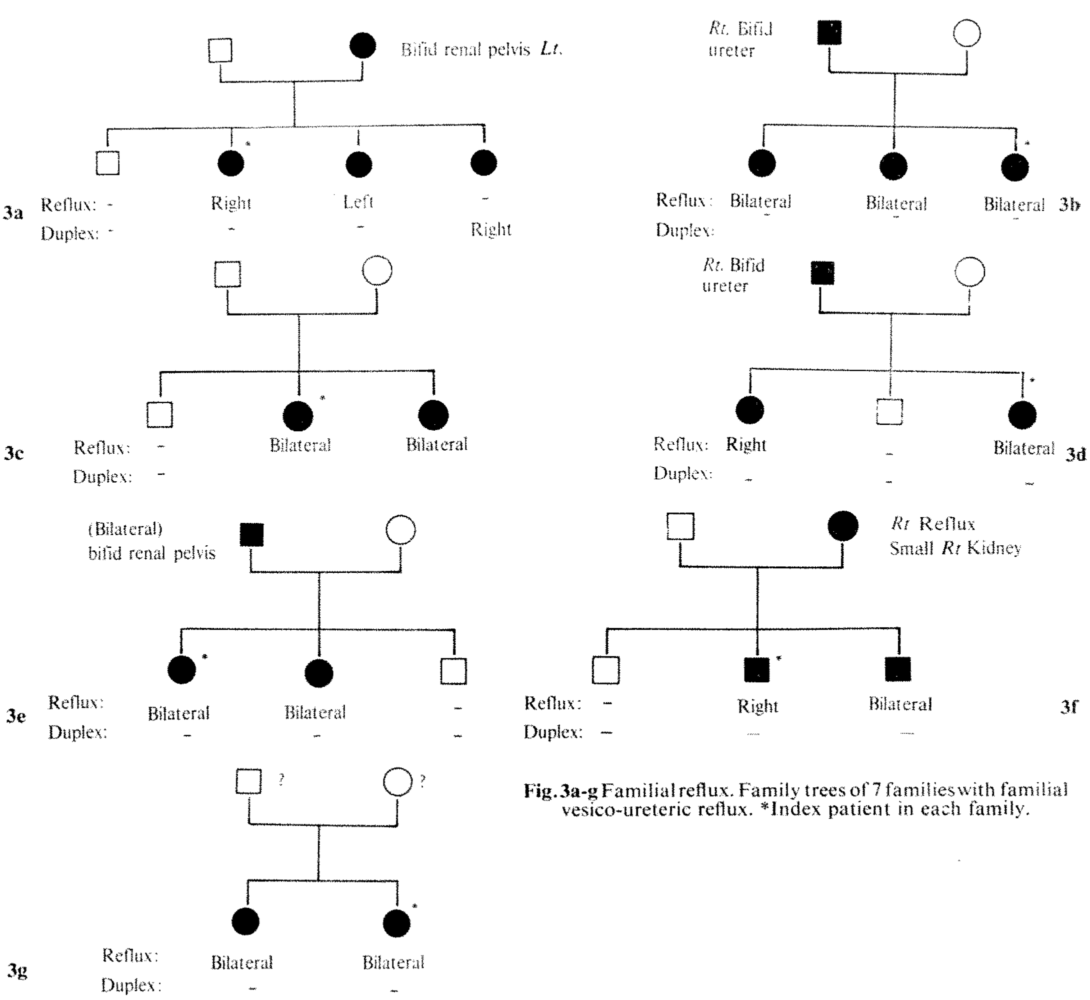


Fig. 3a-g Familial reflux. Family trees of 7 families with familial vesico-ureteric reflux. *Index patient in each family.

ureteric orifice with reflux. There was no difference in the incidence of the radiological findings whether one considered male or female index patients (Male, 3 affected out of 15; Female, 10 affected out of 39 (Table III). In the 22 families where IVPs are available for both parents there were 9 families with 1 affected parent and 13 families with neither parent affected. In the former group, 17 of 26 siblings were found to have reflux or a bifid pelvicalyceal system. In the latter group, 17 of the 35 siblings were similarly affected (Table IV).

In 7 families familial vesico-ureteric reflux was found (Fig. 3a-g). In 4 of them there was duplicity of the pelvicalyceal system in either siblings or parents and in an additional family 1 of the parents had vesico-ureteric reflux. In 6 other families duplicity of the pelvicalyceal system was found in either parents or siblings (Fig. 4a-e). Thus in 13 of the 52 families investigated we found either familial reflux or duplicity of the urinary tract. Full details of each family are given in the Appendix.

Discussion

In our initial investigation of the familial incidence of duplicity of the urinary tract (Atwell

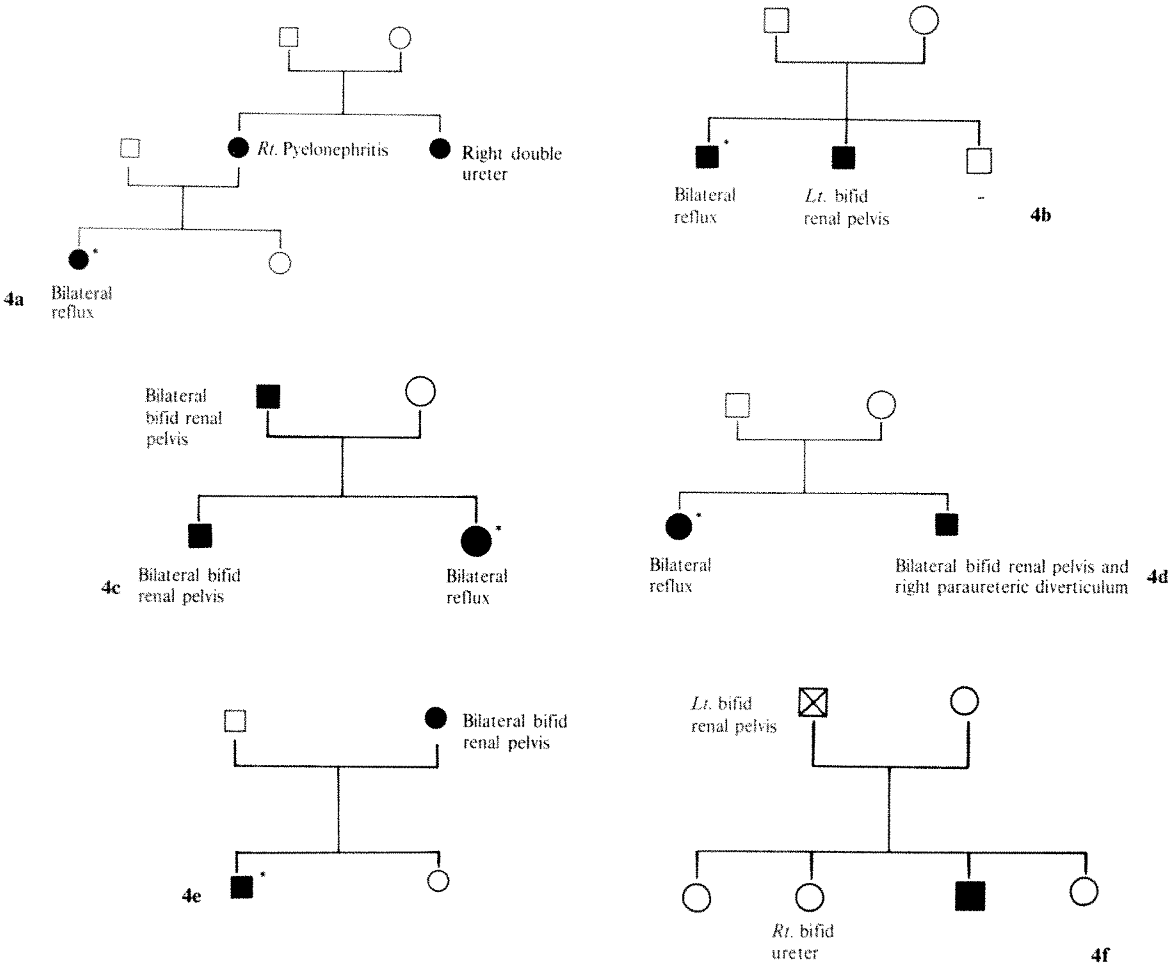


Fig. 4a-f Reflux and Duplex. Family trees of 6 families in whom duplicity of the pelvicalyceal system was found in first-degree relatives. *Index patient in each family.

et al., 1974) we found that ureteric reflux sometimes occurred in the siblings of our duplex patients. In some of these patients the presence of pyelonephritis had not previously been suspected. This finding led directly to the present investigation in order to determine the incidence of various degrees of duplex collecting systems in the first-degree relatives of index patients with primary or idiopathic reflux.

The finding of 8 patients with a bifid pelvicalyceal system, 3 with bifid or double ureters, and 8 with lateral ectopia of the ureteric orifice and reflux, supports the hypothesis that primary reflux may be inherited as an autosomal dominant gene. Further support is provided by the observation that in 9 families with 1 affected parent, 17 of 26 siblings were affected. However, in 13 families without an affected parent 17 of 35 siblings were affected. A possible explanation is that inheritance is by a dominant gene which fails to become manifest in some patients and is therefore of low penetrance.

If this hypothesis is accepted one has to consider the interrelationship between a duplex urinary tract, trigonal anomalies and the causation of vesico-ureteric reflux. There is no doubt that the main factor preventing vesico-ureteric reflux is the length of the intramural part of the ureter (Cass and Ireland, 1972). When a duplex system is present the ureter from the lower moiety of the kidney passes more directly through the bladder wall and this is often associated with pyelonephritis and scarring of the lower pole of the kidney. Reflux to the contralateral non-duplex kidney was found in 23% of our patients with a symmetrical trigone. Furthermore, reflux was unilateral when the trigone showed asymmetry either with or without the presence of a bifid ureter or renal pelvis. These findings suggest that lateral ectopia of the ureteric orifice may be the "common factor" in such cases.

The importance of the position and configuration of the ureteric orifice in relation to vesico-ureteric reflux has been well described in children (Lyon *et al.*, 1969). In adults, similar observations have demonstrated a relationship between renal scarring and the position of the ureteric orifice (Ambrose, 1969; Vermillion and Heale, 1973). The latter author also stated that over 400 vesico-ureteric junctions considered representative of lateral ectopia had been carefully dissected transvesically at the time of reimplantation. Inflammatory reaction or scarring sufficient to produce incompetence by loss of pliability or retraction was not seen. He concluded that faulty development was the only satisfactory explanation for the anatomical defect of lateral ectopia.

Studies of duplicated ureters indicate that early intravesical separation or migration of the ureter from the Wolffian duct results in poor or weak attachment to the trigone with resulting lateral ectopia and that delayed migration enhances its attachment to the Wolffian structures of the trigone and urethra (Ambrose and Nicolson, 1964).

Many authors have noted the familial incidence of vesico-ureteric reflux. The presence of reflux in identical twins similar to those in our reported family (Fig. 1A) has been recorded (Mebust and Foret, 1972). Familial reflux in successive generations has been reported (Tobenkin, 1964). Later, 5 families with hereditary reflux secondary to a defect of the vesico-ureteric junction were reported (Burger and Smith, 1971); these authors also reviewed 15 further families from the literature. Later, 8 further families were reported, 3 of which were found to have duplicated urinary systems, a finding in agreement with our experience (Amar, 1972).

In the 2 family surveys which we have completed (Atwell *et al.*, 1974 and the present series) the results suggest a similar method of inheritance for duplex systems and primary reflux by autosomal genes of variable penetrance. This similar method of inheritance suggests that lateral

Table V

Causation of Vesico-ureteric Reflux—Old and Suggested New Classification

A	B	
Primary	*Primary*	
Idiopathic	Idiopathic	
Trigonal abnormalities	Genetic	Trigonal abnormalities
Familial		Familial
		Duplex ureters
Secondary		Paraureteric diverticulum
Obstruction, e.g. valves		
Hypoplastic: dysplastic kidneys	*Secondary*	
Duplex ureters	Obstruction, e.g. valves	
Neurogenic	Hypoplastic: dysplastic kidneys	
Megaureter megacystis syndrome	Neurogenic	
Inflammation	Megaureter megacystis syndrome	
Para-ureteric diverticulum	Inflammation	
Decompression of a ureterocele	Decompression of a ureterocele	
Release of a stone	Release of a stone	
Associated with megarectum	Associated with megarectum	
Meagureters	Megaureters	

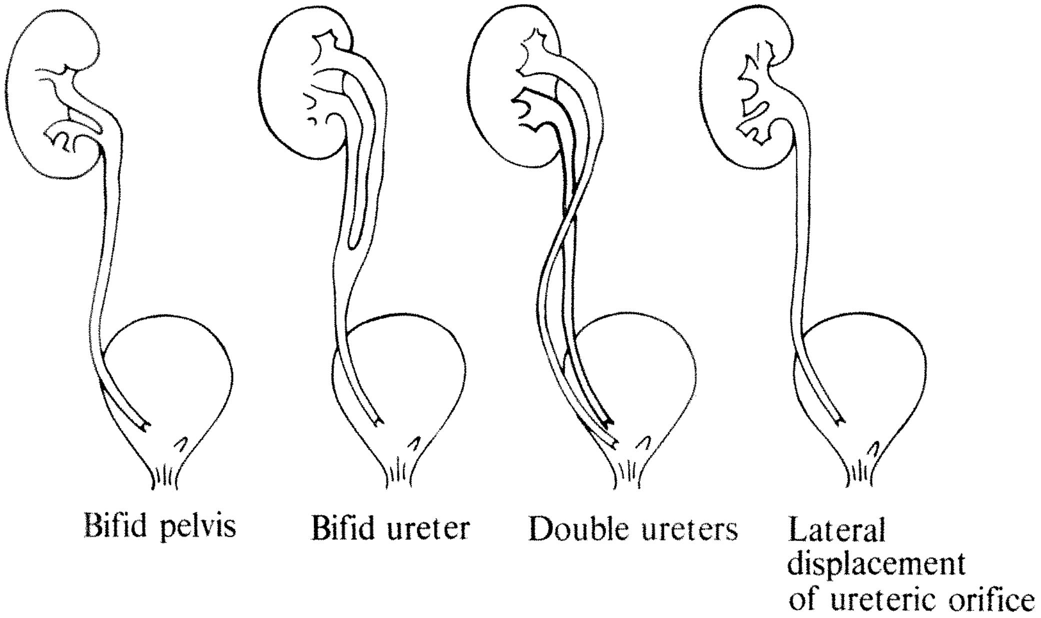


Fig. 5. Classification of the duplex urinary tract suggesting that lateral ectopia of the ureteric orifice should be considered as part of the syndrome of duplicity of the pelvicalyceal system.

ectopia of the ureteric orifice should be considered as an essential component of the syndrome of a duplicated urinary tract (Fig. 5). Other authors have suggested that the length of the intravesical ureter in man is determined by multiple genes of cumulative effect (Burger, 1972). This polygenic method of inheritance could explain how the trait is transmitted in families, the sexual and racial differences and the unilateral and bilateral occurrence of reflux. However, an autosomal dominant method of inheritance with variable penetrance of the gene as suggested by our findings would also correlate well with the clinical and anatomical findings.

There has been 1 prospective study of 24 families (Bredin *et al.*, 1975) in which 8 of 50 siblings examined were found to have vesico-ureteric reflux (16%). These 8 siblings were in 4 of the 24 family groups examined. In these 4 families no patients with infection were found and there was no renal scarring, thus adding further support to the theory of sterile reflux predisposing to the development of urinary infection.

If one accepts the hereditary concept of primary vesico-ureteric reflux a reclassification of the causes of reflux will be required. Idiopathic cases will probably decrease in number with a corresponding increase in the genetic cases as more family groups are evaluated. Table V compares and contrasts an older with a newer more suitable list of the causes of vesico-ureteric reflux.

Summary

3 investigations have been undertaken to study the interrelationship between a bifid pelvicalyceal collecting system, vesico-ureteric reflux and lateral ectopia of the ureteric orifice.

Firstly, in 30 families investigated to confirm the familial incidence of bifid and double ureters there were 3 families in which siblings were found with primary reflux.

Secondly, reflux was found in 62 of 110 patients investigated with a duplex pelvicalyceal system. Reflux was to the ipsilateral kidney in 48 patients but occurred to the contralateral kidney, unaffected by duplicity, in 14. This high incidence of reflux is related to lateral ectopia of the ureteric orifice which may be either bilateral or unilateral.

Thirdly, the incidence of a bifid pelvicalyceal system was determined in the parents and siblings of a series of 32 patients with primary reflux. The results support the hypothesis that primary reflux may be inherited by an autosomal dominant gene of variable penetrance in a manner similar to the inheritance of a duplex urinary tract. Thus there is a direct genetic relationship between primary vesico-ureteric reflux, lateral ectopia of the ureteric orifices and a duplex pelvicalyceal system.

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The Authors

J. D. Atwell, FRCS, Consultant Paediatric Surgeon.
P. L. Cook, DMRD, FFR, Consultant Radiologist.
Lesley Strong, BM, Medical Student, University of Southampton.
I. Hyde, FRCP(Ed), DCH, FFR, Consultant Radiologist.

Address for reprints: J. D. Atwell, Wessex Regional Centre for Paediatric Surgery, Southampton General Hospital, Tremona Road, Southampton.

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Appendix

Details of Patients and Families

Family No. and sex of index patient	Index patient	Parents		Siblings	Remarks
		Father	Mother		
S.S. (M)	Rt. double ureters Rt. lower pole	–	–	2 sisters NAD 1 sister bilateral reflux	Families Nos. 9, 12, 17 reported in Atwell *et al.* (1974)
A.Y. (F)	Rt. double ureters Bilateral reflux	Rt. bifid renal pelvis	– –	2 sisters NAD 2 sisters—bilateral reflux 1 brother NAD 1 brother—bilateral bifid renal pelvis and Rt. reflux	
K.B. (F)	Rt. double ureter Lt. bifid ureter Bilateral reflux	–	–	1 sister NAD 1 sister bilateral reflux	
1. (F)	Rt. reflux Bilateral pyelonephritis	–	Lt. bifid renal pelvis	1 brother NAD 1 sister Lt. reflux 1 sister Rt. duplex ? complete ? incomplete	Familial reflux
2. (F)	Bilateral reflux	Rt. bifid ureter	–	2 sisters with bilateral reflux	Familial reflux
3. (F)	Bilateral reflux	–	–	1 brother—abnormal pelvicalyceal system — ? type 1 sister—bilateral reflux	Familial reflux
4. (F)	Bilateral reflux	Rt. bifid renal pelvis	–	1 brother NAD 1 sister Rt. reflux	Familial reflux
5. (F)	Bilateral reflux	Bilateral bifid renal pelvis	–	1 brother NAD 1 sister—bilateral reflux	Familial reflux
6. (M)	Bilateral reflux	–	Rt. reflux	1 brother NAD 1 brother—bilateral reflux	Familial reflux Maternal grandfather with Rt. duplex
7. (F)	Bilateral reflux	No X-ray	–	1 sister—bilateral reflux	Familial reflux
8. (F)	Bilateral reflux	–	Rt. pyelonephritis	1 sister NAD	Maternal aunt with double ureters
9. (M)	Bilateral reflux	–	–	1 brother NAD 1 brother Lt. bifid renal pelvis	–
10. (F)	Bilateral reflux	Bilateral bifid renal pelvis	–	1 brother—bilateral bifid renal pelvis	–
11. (F)	Bilateral reflux	–	–	1 brother—bilateral bifid renal pelvis	–
12. (M)	Lt. reflux	–	Bilateral bifid renal pelvis	1 sister NAD	–

Appendix (Continued)

Family No. and sex of index patient	Index patient	Parents Father	 Mother	Siblings	Remarks
13. (M)	Rt. reflux	–	–	2 sisters NAD 1 sister—Rt. bifid ureter	–
14. (F)	Bilateral reflux	–	–	3 sisters NAD	–
15. (F)	Lt. reflux	–	–	1 brother NAD 1 sister—no X-ray	–
16. (M)	Bilateral reflux	–	–	1 sister NAD	–
17. (F)	Bilateral reflux	–	–	1 sister NAD	–
18. (F)	Rt. reflux	No X-ray	No X-ray	2 sisters NAD 1 sister Lt. renal agenesis	–
19. (F)	Rt. reflux	No X-ray	No X-ray	2 brothers NAD	–
20. (F)	Rt. reflux	–	–	1 brother NAD 1 sister NAD	Maternal aunt with duplex and reflux
21. (M)	Bilateral reflux	No X-ray	No X-ray	2 sisters NAD 1 brother—no X-ray	–
22. (F)	Bilateral reflux	–	No X-ray	2 brothers NAD	Cousin (on mother's side) with pyelonephritis
23. (F)	Bilateral reflux	–	–	1 brother NAD 1 sister NAD	–
24. (M)	Bilateral reflux	–	–	1 brother NAD	–
25. (F)	Bilateral reflux	No X-ray	No X-ray	–	Cousin with duplex
26. (F)	Lt. reflux	–	–	1 brother NAD 1 sister NAD	–
27. (F)	Lt. reflux	–	–	3 brothers NAD	–
28. (F)	Bilateral reflux	–	No X-ray	2 brothers NAD	–
29. (M)	Bilateral reflux	No X-ray	No X-ray	1 sister NAD	–
30. (F)	Lt. reflux	No X-ray	No X-ray	1 sister NAD	–
31. (F)	Lt. reflux	No X-ray	No X-ray	1 sister NAD	–
32. (M)	Bilateral reflux	No X-ray	–	1 brother NAD 1 sister NAD	–

M = Male. F = Female.

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Short Case Report

Milk-of-Calcium in a Renal Cyst

Case Report

A 30-year-old welder presented with severe backache of 4 months' duration. Physical examination and routine investigations, including calcium studies, revealed no abnormality. A cyst, 8 × 5 cm in size, was seen in the lower pole of the left kidney (Fig. 1). In the erect position, the opaque contents of the cyst appeared to sediment and form a discrete layer (Fig. 2). Intravenous pyelogram showed compression of the calyces of the lower pole of the left kidney. Under local anaesthesia the cyst was punctured and 130 ml of straw-coloured fluid removed. A crystalline deposit which rapidly settled was made up of "microliths" showing a circular laminated appearance and consisting mainly of calcium phosphate.

6 months after aspiration, there had been no significant recurrence of symptoms.

Comment

"Milk-of-calcium" describes a fine suspension of calcium salts in solution which precipitate in the most dependent part of a cyst cavity, producing a characteristic radio-opaque shadow with a sharp fluid level varying with the position of the patient. This phenomenon is well recognised in gall bladder disease but less than 20 patients have been described with the condition occurring in relation to the kidney (Murray, 1970; Pomerantz, Kirschner, and Twigg, 1970).

Clinical presentation has included backache and ureteric colic due to sediment being dislodged from the cyst, but most occur as an incidental finding on X-ray or at autopsy. In the presence of symptoms related to such a cyst, treatment has usually been by aspiration, but persistent pain, infection, or haematuria, may necessitate surgical treatment (Sanidad, Miller, and Mendelsohn, 1969).

W. R. Dimitri, J. A. K. Meikle and A. I. G. Davidson
Department of Surgery, Perth General Hospitals

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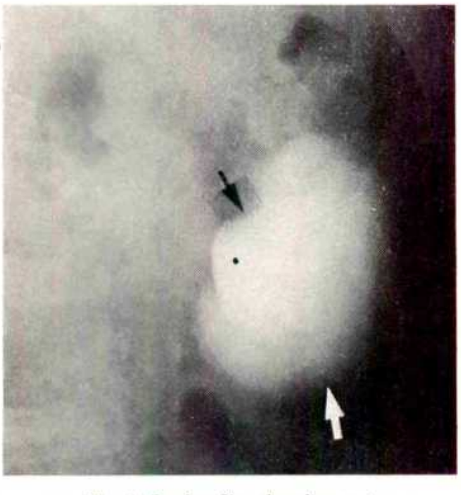

Fig. 1. Supine film showing cyst.

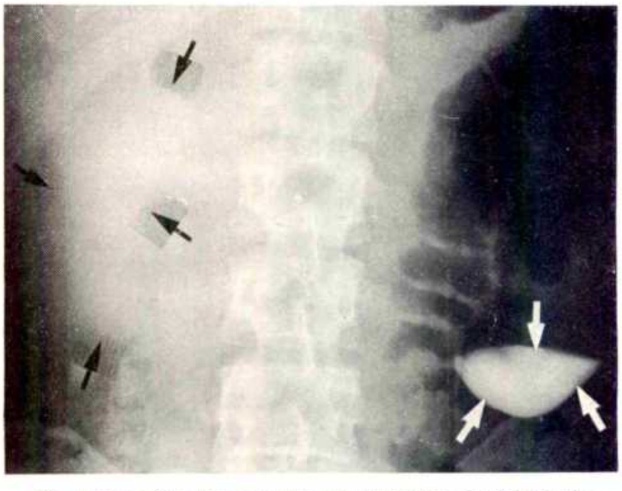

Fig. 2. Erect film demonstrating precipitation of calcium salts.

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The Management of Ureteric Reflux in Children

JOHN E. S. SCOTT

Department of Surgery, University of Newcastle upon Tyne

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Despite a considerable volume of literature on the subject of vesico-ureteric reflux in children, there are still certain questions that remain unanswered. Most notable are those related to the natural history of the disease, its age of onset, the age at diagnosis and the long-term outcome of both operative and non-operative treatment. The purpose of this paper is to provide some of the answers by studying data obtained from an analysis of a personal series of 262 children suffering from reflux.

The series includes all children referred to the author between December 1960 and January 1974 with a diagnosis of reflux uncomplicated by obstructive lesions in the urinary tract. Children whose reflux was associated with conditions such as posterior urethral valves or neurogenic bladder were excluded.

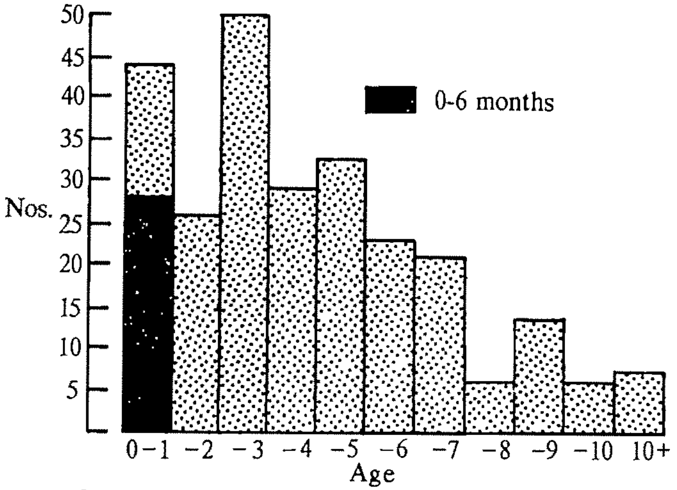
Sex Distribution

There were 197 girls and 65 boys, a female to male ratio of 3/1. The sex incidence of urinary infection in children is identical (Stansfeld, 1966; MacGregor and Freeman, 1975).

Age at Onset of Symptoms (Table I)

Symptoms in all children except 2 were caused by the onset of urinary infection; the 2 exceptions presented with enuresis. In only 1 child was the recorded history so imprecise that it was impossible to pinpoint the moment when significant symptoms first occurred.

Table I



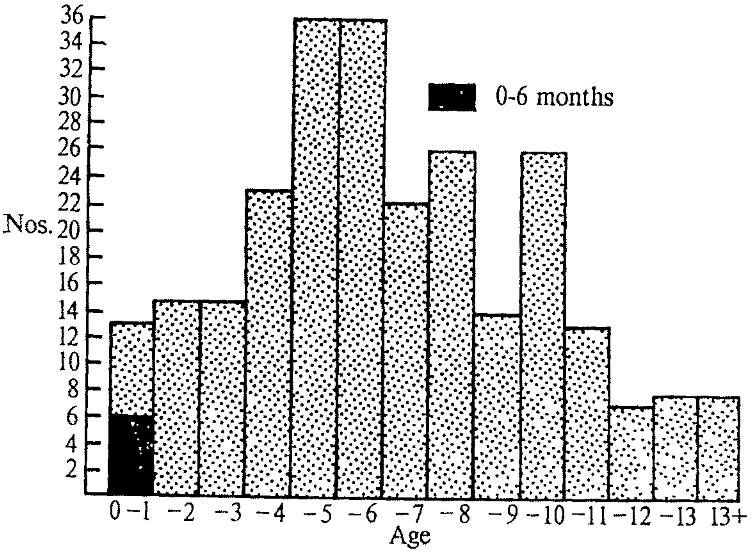
2 cases never infected 1 case history unreliable

The peak incidence was between 2 and 3 years and 182 (69·5%) developed symptoms before the age of 5 years a figure which again is similar to that found by Stansfeld (1966) and MacGregor and Freeman (1975). Stansfeld's series contained children with urinary infection of mixed aetiology but MacGregor and Freeman separated children with reflux from the remainder in their series and found that in the former symptoms of urinary infection started earlier than in the latter.

Age at Diagnosis (Table II)

The table shows the ages of the children when reflux was first diagnosed by cystographic examination.

Table II

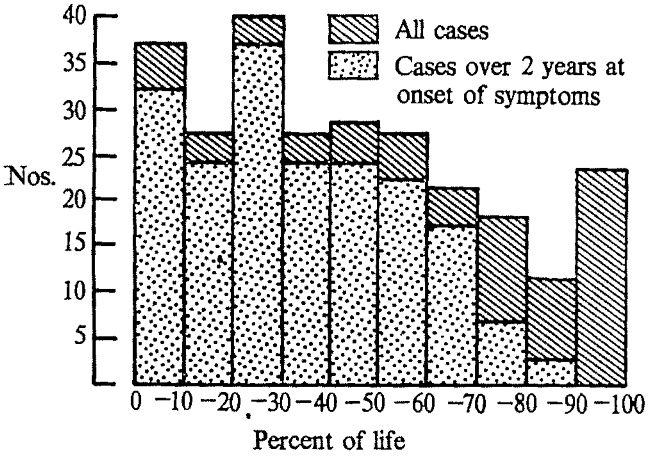


The diagnosis was most often made between 4 and 6 years and, by contrast with the age at onset of symptoms, only 102 children (39%) were diagnosed before the age of 5 years. Thus in only 56% of the children whose symptoms began in the pre-school years was the reflux discovered before starting school.

Time Interval between Onset of Symptomatic Urinary Infection and Diagnosis of Reflux (Table III)

Where reflux is concerned symptoms of 1 year's duration in a child of two may have different

Table III



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implications from symptoms of the same duration in a child of 10. It was decided, therefore, to express the duration of symptoms as a percentage of each child's age at the time reflux was diagnosed (Table III).

It is noteworthy that in the whole series, 100 children (38·2%) had symptoms for over half their lives before reflux was diagnosed and that even if the under-two-year-olds are excluded the proportion is 25·4%. This reinforces the previous finding that urinary infection in the children included in this series was allowed to continue for a long time before appropriate investigations were undertaken.

Type of Reflux (Table IV)

Approximately equal numbers of children had reflux unilaterally and bilaterally though there were 12 in whom reflux varied from one side to the other during the time they were under supervision. Rolleston, Shannon and Utley (1970) also found equal numbers with unilateral and bilateral reflux in their series of infants.

Table IV

Reflux

Unilateral	142	
Bilateral	120	
Unilat.⇌Bilat.	12	
Duplex	**Unilat.**	**Bilat.**
Lower pole	23	12
Upper pole	2	0
Both poles	8	5
Grade	**Male**	**Female**
I	18	148
II	47 (72·3%)	49 (24·9%)

Table V

Scarring

Unilateral	110	177 (67·6%)
Bilateral	67	
Unilat.→Bilat.	1	
8 with scarring on non-refluxing side as well as refluxing side		
Male	50 (76·9%)	
Female	127 (64·5%)	

Table VI

Reflux and Scarring

Of 142 non-refluxing kidneys:
8 were scarred;
134 had no scarring

Of 382 refluxing kidneys:
238 were scarred;
144 had no scarring

37 (14%) children had duplications of the upper urinary tract and, as expected, reflux occurred into the ureter from the lower component in the majority (Williams 1968). Those with reflux into both ureters of duplex systems had short common terminal ureteric segments which entered the bladder through a single incompetent orifice.

Reflux was graded according to the system advocated by the author (Scott, 1972). Only 2 grades are used, the second being allotted to children with massive reflux into dilated ureters for which surgery is clearly indicated. The first grade is for children whose reflux is less severe and may, in time, disappear spontaneously.

96 (36·6%) children had reflux which at diagnosis was severe enough to be classified as grade 2. More interesting was the fact that 72·3% of the boys compared with only 24·9% of the girls fell into this category, confirming the

author's contention, expressed previously (Scott, 1972, 1975), that reflux has a more serious effect on the upper urinary tract in boys; this is probably due to the higher flow resistance of the male urethra as compared with the female.

Scarring of the Renal Parenchyma (Tables V and VI)

The presence of parenchymal scarring as described by Hodson and Edwards (1960) and Hodson and Wilson (1965) was assessed from the appearance of the kidneys on intravenous pyelography.

A total of 177 (67·6%) children had scarred kidneys, an approximately similar incidence to that quoted in the reports of Scott and Stansfeld (1968) and Hutch, Chisholm and Smith (1969), but double the figure given by Smellie *et al.* (1975). 110 children had scarring in only 1 kidney and both kidneys were scarred in 67. There was 1 child who had unilateral scarring when first investigated but developed bilateral scarring later and there were 8 children with unilateral reflux who showed evidence of scarring in the kidney on the non-refluxing side as well as the refluxing side. Although there was a higher proportion of boys with stage 2 reflux, the difference between the sexes with regard to scarring was much less.

Table VI shows the relationship between reflux and scarring and emphasises the high incidence of scarring in kidneys affected by reflux as opposed to those without. The distribution of ages at onset of symptoms in children with scarred kidneys did not differ from the series as a whole.

Hypertension

Significant hypertension (diastolic blood pressure above 12 kPa (90 mm Hg)) was present in 4 children at the time reflux was diagnosed and a further 6 developed hypertension later. 4 were subjected to nephrectomy with complete resolution of the hypertension in 2. The remainder, with the exception of 1 who has mild asymptomatic hypertension, are either on anti-hypertensive drug therapy or under treatment for chronic renal failure. The important features are that 4% of all the children in the series became hypertensive as a result of their disease and that anti-reflux surgery did not prevent the onset of hypertension.

However, if hypertension in a child with reflux can be controlled with the appropriate drugs and if the child is subject to recurrent urinary infections which may produce further renal damage, anti-reflux surgery is indicated despite the hypertension.

Renal Failure

16 children had evidence of renal failure at the time of diagnosis which was moderate (plasma urea between 7 mmol/1 (40 mgm/100 ml) and 13 mmol/1 (80 mgm/100 ml)) in 13 and severe (plasma urea above 13 mmol/1 (80 mgm/100 ml)) in 3. A further 3 children whose kidneys were already severely damaged by the time of operation developed renal failure later. Thus a total of 7·8% of the children in this series developed renal failure which was permanent in 5·3%.

Renal failure does not contra-indicate anti-reflux surgery, indeed 5 children with depressed renal function improved after operation and a further 6 were stabilised. However, it is important that facilities for treating acute renal failure in children are readily available before embarking on surgery in such cases.

Management

All children with known or suspected ureteric reflux were admitted to hospital for investigation which comprised complete physical examination, blood count, plasma urea, creatinine and electrolyte levels, urine culture, cystography and intravenous pyelography.

The indications for surgical treatment have been described previously (Scott, 1972, 1975), but briefly, operation was advised for most boys, pre-school children, children with grade 2 reflux, kidney scarring, additional urinary tract anomalies or a history of recurrent urinary infection unresponsive to antibacterial drugs. Cystoscopy was not performed when a definite decision to operate was made on one or more of the above criteria. In all other cases, however, the cystoscopic appearance of the ureteric orifices was the final evidence required to make a decision for or against operation; for example, a child whose ureteric orifices were normal or near-normal, was managed conservatively in the first instance.

After discharge from hospital the children were followed in the outpatient clinic and antibacterial therapy managed on the basis of low dosage courses of 6 to 12 months' duration (Scott and Stansfeld, 1968; Scott, 1969) according to the child's proneness to become reinfected. Approximately 1 year after the initial admission the children were readmitted for review intravenous pyelography and cystography. Postoperative cases in whom these investigations were satisfactory were again followed in the out-patient clinic where their antibacterial therapy was continued as above. Subsequent intravenous pyelograms were done after intervals of 3 and 6 years. Management of the non-operated cases whose reflux had disappeared was continued in the same manner as the operated cases, but for those whose reflux persisted a decision was made either to operate or to continue conservative management for a further year. This decision was based on the propensity of the child's urinary infection to recur after cessation of antibacterial therapy during the observation year and the change, if any, that had taken place in the degree of reflux. For example, a child whose urine had remained sterile after the antibacterial drugs were stopped and whose reflux was diminishing was managed conservatively for a further year but if the infection had recurred and the reflux had converted from unilateral to bilateral, operation was recommended. The children with persistent reflux who were not operated on were reinvestigated at the end of the second or subsequent observation years until reflux disappeared.

156 (59·5%) children were treated primarily by operation and 107 (40·8%) conservatively. 1 child with bilateral reflux appeared in both groups because only 1 ureter was operated on initially and the other after 1 year's observation. Of the children initially managed conservatively, 34 (32%) were subsequently operated upon; thus in only 27·9% of the whole series was it possible to persist with conservative treatment throughout.

Re-operation because the first had failed to eliminate reflux was performed in 4 children. 31 (11·8%) required nephrectomy because the kidney was beyond salvage.

Reflux remained unchanged in 14 children and increased in 21 and of 16 who had unilateral reflux when first investigated 9 became bilateral.

When the distribution of reflux and scarring between the operated and conservative cases was analysed it was found that only 4 children treated conservatively had grade 2 reflux but 40 (54·8%) had normal kidneys, compared with 32 (13·5%) in the operated group. This latter figure is biased by 11 children from a previous series who were selected for operation at random (Scott and Stansfeld, 1968).

Results

20 children were unavailable for follow-up, either because they could not be traced or because they had not been subjected to review cystography. None had been treated by operation.

Surgery: Reflux

The operative technique was based on the methods of Politano and Leadbetter (1958) and Paquin (1959) and has been described previously (Scott, 1969).

Of 163 children subjected to anti-reflux surgery, reflux was eliminated on the operated side in all but 6; 4 of these were re-operated, giving a total success rate of 98·8%. However, of 59 children operated unilaterally, reflux appeared on the contralateral side in 11 (18·6%). 2 of these children were successfully re-operated upon and in 5, the reflux subsequently disappeared spontaneously. The remaining 4 are still under supervision with persistent reflux in the unoperated ureter and have not, as yet, developed another urinary infection.

Dilatation of the operated ureter in the follow-up intravenous pyelogram was apparent in 9

(5·5%) children. 1 child had a solitary kidney which was grossly dilated preoperatively and it was decided that a surface diversion should be carried out to prevent further renal damage. Of 5 others with mild dilatation complete resolution occurred after a further 6 months in 3; the remaining 2 were awaiting a second postoperative pyelogram at the time of follow-up. The dilated ureter was re-explored in 3 children, one of whom had been reported previously (Scott, 1969). In both the other 2, it was the left ureter which was involved. At re-exploration it was found that the peritoneum, including in 1 case the small bowel mesentery, had been transgressed in the process of re-routing the ureter through the bladder wall so that a stricture had formed at the point where the ureter passed through the peritoneum. This accident has occurred in the hands of other operators (Price, Johnston and Marshall, 1970) and is clearly a technical failure which extra care

Table VII

Results—Surgery: Infection

No. of recurrences	No. of children	No. on treatment	No. of children by length of follow-up							Length of time off treatment		
			<1	1-2	2-3	3-4	4-5	5-6	>6	<1	1-2	>2 years)
0	81	4	2	8	10	22	16	4	19	5	14	58
1	31	9	1	3	4	7	2	5	9	4	2	16
2	14	4	0	0	1	3	2	2	6	2	3	5
3	11	4	0	0	1	3	1	1	5	1	3	3
4 or more	26	13	0	2	1	2	1	1	20	6	6	7
Total	163	34	3	12	17	37	22	13	59	12	28	89

60% off treatment more than 2 years at follow-up.
Of 148 children followed more than 2 years, 98 (66%) had no recurrence or only 1, and 36 (24%) had 3 or more recurrences.

Table VIII

Possible Reasons for Recurrences of Infection (Operated Cases)

Sex		*Age at onset of symptoms*		
Male	4 (7·8%) [24·8%]	Below 5 years		38 (74·5%) [69·5%]
Female	47 (92·2%) [75·2%]	Above 5 years		13 (25·5%) [29·4%]
Grade of Reflux+Laterality		*Length of life (%) between Onset of Symptoms and Diagnosis*		
Grade I	39 (76.5%) [64·4%]	More than 50%		18 (35·3%) [38·2%]
Grade II	12 (23·5%) [36·6+]	Less than 50%		33 (64·7%) [61·4%]
Unilat.	21 (41·2%) [54·2%]			
Bilat.	30 (58·8%) [45·8%]			
Failure to Eliminate Reflux		*Scarring*		
On operated side	0	Present	Unilat. 83	(60·8%) [67·6%)
Reflux persisting at follow-up	0		Bilat. 13	
Persistent dilatation	0	Absent	20	(39·2%)

Children with two or more recurrences 58 (38·3%)
All children in series [ ]

should avoid. In the 2 cases in question, the ureters were re-mobilised and re-implanted again with satisfactory resolution of the dilatation.

Infection (Table VII)

The effectiveness of combined medical and surgical treatment in eliminating urinary infection was measured by the number of recurrences which occurred. Clearly the longer a child was followed, the stronger was the chance of reinfection and so each group was analysed by length of follow-up. The number of children having antibacterial therapy at the time of follow-up was recorded together with an analysis of the length of time each group had been off treatment.

The most important features to emerge from the analysis in Table VII are that 66% of the children followed for more than 2 years had no, or only 1, recurrence of infection and that 24% had 3 or more. Only 60% had been off treatment for more than 2 years at the time of follow-up.

The children who developed 2 or more reinfections were compared with the series as a whole (Table VIII). It is noteworthy that none of these children had persistent reflux or postoperative ureteric dilatation, indeed the only outstanding feature was that almost all the "relapsers" were girls. In addition, though to a smaller degree, there were differences with regard to the grade of reflux and its laterality, there being more with grade 1 reflux, which seems paradoxical, and more with bilateral reflux, which seems logical. There were no significant differences in any of the other factors examined.

Nephrectomy

25 children were subjected to nephrectomy as the only form of surgical treatment: 15 had single ureters and 10 duplex. The ureter was removed completely in each case to prevent reflux into the stump. Despite complete removal of the diseased part of an otherwise normal urinary tract, nearly 19% of this group of children continued to develop recurrences of infection.

Conservative Treatment Only

54 children were available for follow-up study and of these only 6 were boys, which emphasises the tendency for them to develop severe reflux and be selected for operation. Reflux disappeared completely in 34 (63%) children (14 of 21 with bilateral reflux and 20 of 30 with unilateral reflux). Of the 20 children in whom reflux persisted, 14 had been followed for more than 3 years at the

Table IX

Results—Conservative Treatment: Infection

No. of recurrences	No. of children	No. on treatment	No. of children by length of follow-up							Length of time off treatment		
			<1	1-2	2-3	3-4	4-5	5-6	>6	<1	1-2	>2
0	24	1	1	5	4	3	4	1	6	2	5	16
1	9	1	0	0	2	0	2	1	4	0	2	6
2	7	2	0	0	0	1	2	3	1	1	1	3
3	6	2	0	0	1	1	0	1	3	1	0	3
4 or more	8	3	0	0	0	2	0	0	6	0	0	5
Total	54	9	1	5	7	7	8	6	20	4	8	33

68·8% off treatment more than 2 years at follow-up.
Of 48 children followed more than 2 years, 27 (56·3%) had no recurrence or only 1, and 14 (29·3%) had 3 or more recurrences.

time the study was completed and more than 2 years had elapsed since their last infection. Conservative management was deemed not to have failed in these cases but to be worth continuing.

Infection (Table IX)

The infection recurrence rate is tabulated in the same manner as for the children treated by surgery. The number of children who had been off antibacterial therapy for more than 2 years at the time of follow-up was 68·8 %, slightly more than the operated group, and of the children followed more than 2 years, 56·3% had no, or only 1, recurrence and 29·2% had 3 or more. This indicates a slightly higher reinfection rate in the conservatively treated children.

The recurrence rate in the children followed more than 2 years was correlated with the incidence of spontaneous disappearance of reflux (Table X). Reflux completely disappeared in 55% of the children who had no, or only 1, recurrence but paradoxically in 78·6% of the children who had three or more.

Table X

Results—Conservative Treatment: Infection and Reflux
(Children followed more than 2 Years)

No. of recurrences	No. of children	Spontaneous disappearance	
		Completely	One side only
0	**18**	**11**	1
1	**9**	**4**	3
2	7	5	1
3	**6**	**4**	0
4 or more	**8**	7	0

Of 27 children with no recurrence or only one, reflux disappeared completely in 15 (55%).
Of 14 children with 3 or more recurrences, reflux disappeared completely in 11 (78·6%).

Table XI

Results—Conservative Treatment Only

(Time during which reflux disappeared spontaneously from original diagnostic cystogram)

Duration (years)	No. of Cases	
1-2	11	
2-3	10	
3-4	9	18 = 46·2%
4-5	2	
>5	7	

The length of time taken for reflux to disappear in the conservatively treated children is shown in Table XI. It is noteworthy that in nearly half the children more than 3 years elapsed before their reflux disappeared.

Discussion

It appears from this study that symptoms in children with urinary infection and ureteric reflux usually start before the age of 5 years, yet the reflux remains undiagnosed until after this age. As a consequence, a significant proportion of children have symptoms for more than half their lives before they are properly investigated and the true nature of their disease comes to light. It is in these early years when uncontrolled infection is reaching the kidney that the destruction of the renal parenchyma is initiated. If the renal damage which is so commonly seen pyelographically in older children is to be prevented the correct diagnosis must be established as soon as possible after symptoms first occur. Although, in some instances, parents may fail to seek medical advice, it is the family doctors who must bear the responsibility for suspecting a urinary infection in any ill young child and for examining the urine accordingly. As a corollary, it seems logical to assume that if symptomatic bacteriuria associated with reflux occurs commonly in the pre-school child, then the search for asymptomatic bacteriuria in the same age group would be more profitable than in the school-age child.

The incidence of hypertension and renal failure in this series emphasises the serious nature of the disease and the need for early diagnosis and prompt treatment.

It has been shown that (even in the hands of a surgeon) over two-thirds of the cases selected for conservative management had a satisfactory outcome. However, it is important to note that the younger the child at the time of diagnosis, the greater is the chance of preventing renal damage. It may not be possible to determine from the pyelogram of a young child whether or not such damage has already taken place, since not until an interval of several years has passed will differential growth in the kidney reveal the scarred areas. Thus a normal pyelogram does not contra-indicate anti-reflux surgery in the young child; this may indeed be an opportunity permanently to protect the kidney at an early age from future urinary infections.

The results of surgery in eliminating reflux are satisfactory and the morbidity rate minimal. There were slightly fewer reinfections in the surgically treated cases, some of whom were specially selected for this form of treatment because of this tendency. Moreover, the group also included a number of the conservatively treated cases who continued to have infections despite adequate antibacterial therapy.

More than 3 years elapsed before reflux disappeared in nearly half the conservative cases, indicating that in the absence of infection or when infection can easily be controlled it is worth persevering with this form of management. However, it is essential that the reflux is in grade 1, that the ureteric orifices are cystoscopically normal or near-normal and that there are no other structural abnormalities in the urinary tract before embarking on such prolonged observation. The unexpected finding that reflux disappeared spontaneously more often in the children with a higher reinfection rate shows that the single important factor governing this phenomenon is time. Needless to say, it cannot be deduced that reflux is more likely to disappear because infection is recurring: all these children were under close supervision and each recurrence was detected and treated without delay. Most of these children were in the older age groups and many already had scarred kidneys; had they been diagnosed when they were younger. an operation might well have prevented the scarring.

Summary

A series of 262 children suffering from vesico-ureteric reflux is presented. Nearly all presented with a urinary tract infection and the age at onset of symptoms was predominantly in the pre-school years. The reflux was not diagnosed in the majority until after the children started attending school. Over one-third had symptoms for more than half their lives before reflux was diagnosed.

The incidence of hypertension and renal insufficiency in the series were 4% and 7·8% respectively.

Nearly 60% of the children were selected by defined criteria for operation as their initial

treatment. The remainder were treated conservatively in the first instance but 30% of these subsequently required operation.

Reflux was eliminated in 96·3% of the children at the first operation and 5·5% developed postoperative ureteric dilatation, none of them permanently. Reflux disappeared spontaneously in two-thirds of the children treated conservatively but took more than 3 years in 46%.

Infection recurred in 24% of children treated by operation and in 29% treated conservatively.

The incidence with which reflux disappeared spontaneously in the children treated conservatively was related to time, not to the infection recurrence rate.

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The Author

John E. S. Scott, FRCS, Senior Lecturer in Paediatric Surgery.

Address for reprints: Department of Surgery, University of Newcastle upon Tyne, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP.

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Vesico-ureteral Reflux in Children

BENT E. JAKOBSEN, HELGE GENSTER, SIGURD OLESEN and ERLING NYGAARD
Department of Surgery K (Urology), University Hospital, Aarhus, Denmark

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Operative techniques for the correction of vesico-ureteral reflux, and modifications of these (Grégoir, 1957; Bischoff, 1958; Politano and Leadbetter, 1958), have resulted in cessation of the reflux in up to 96% of the cases.

Only during recent years have studies appeared on the course of untreated or conservatively treated reflux (Smellie and Normand, 1968; Williams, 1971; Ericsson, 1976), and even though our knowledge of this is still limited, it constitutes a valuable supplement to the many reports of the results obtained by surgical treatment.

The purpose of the study presented here was to investigate the effect of treatment on (1) the reflux, (2) changes in the urograms, particularly in the pelvic and ureteral dilatation and parenchymal scarring, (3) the symptoms of the patients, and (4) the frequency of occurrence of bacteriuria.

Material and Methods

A prospective study has been performed on vesico-ureteral reflux in 126 children consecutively admitted to this department during the period 1966-74.

Table I

Age and Sex Distribution of 126 Children with Vesico-ureteral Reflux Treated in the Period 1960-74

Age, in years	0-6/12	7/12-2	3-5	6-8	9-12	Total
Girls	3	5	20	43	23	94
Boys	11	7	4	5	5	32
Total	14	12	24	48	28	126

Table II

Grading of Reflux in 193 Renal Units Related to the Frequency of Renal Scarring

		No. of units	Renal scarring	
			No.	%
Grade I	Reflux to ureter, without dilatation	41	2	5
Grade II	Reflux to ureter and pelvis, without dilatation	68	15	22
Grade III	Reflux to ureter and pelvis, with dilatation	84	23	28
Total		193	40	21

The age and sex distribution of the patients is shown in Table I. The series consisted of 94 girls and 32 boys. The 3 oldest age groups showed a female preponderance, but up to 2 years there were more boys than girls.

Before treatment, all patients were subjected to the following investigations: urography, micturating cysto-urethrography, blood chemistry, urine culture, urethro-cystography and, as far as the girls were concerned, measurement of the calibre of the urethra by means of bougies à boule.

Urological Status

The presenting symptoms appear in Table XI. Table XII shows the occurrence of pre-treatment bacteriuria and gives a survey of previous antibacterial therapy. The pre-treatment urographic findings are listed in Table X.

Many of the children had a duplex kidney on one or both sides, and in a number of cases reflux occurred only to some of the renal units. In the 126 children, a total of 193 renal units with vesico-ureteral reflux were encountered. In Table II, the grades of reflux in the 193 units, classified by the method of Rolleston, Shannon and Utley (1970), are related to renal scarring (reflux nephropathy). It is seen that the frequency of scarring increases with the severity of the reflux.

In 100 renal units, the reflux could be unquestionably classified as primary, as the ureteral orifices were larger than normal with an abnormally short submucous course and an under-developed trigonal area. In 60 units, the reflux was classified as secondary to infravesical obstruction. In the remaining 33 units, the reflux could not be definitely classified.

All but 9 of the children had normal serum creatinine levels.

Treatment

The indications for surgical treatment were largely as follows: (1) infravesical obstructions were corrected surgically in all cases; (2) patients with primary reflux, grades I and II, were subjected to operation when several courses of long-term antibacterial therapy had failed to give sterile urine or eliminate pyelonephritic episodes; (3) all patients with grade III reflux were subjected to operation.

A survey of the results of treatment in the 126 children is given in Table III. Conservative treatment only was used in 13 cases (10%). Infravesical obstructions were removed in 30 cases (25%). In 11 of these cases Y-V plasty on the bladder neck was performed, while the remaining

Table III

Results of Treatment assessed by Micturating Cystography in 126 patients

	Total No. of patients	Reflux after definitive treatment					Miscellaneous (No. of patients)
		Eliminated		Diminished		Unchanged	
		No.	%	No.	%	No.	
Medical treatment only	13	7	54	1	–	2	3[1]
Surgery on the urethra	30	21	70	6	20	3	
Reimplantation of the ureter							
Leadbetter technique	78	67	86	8	10	–	3[2]
Bischoff technique	2	1	–	–	–	1	–
Nephrectomy/ileal loop	3	–	–	–	–	–	3[3]
Total	126	96	76	15	12	6	9

[1] 2 died, 2 not followed.

[2] 1 died, 2 not followed.

[3] 2 nephrectomy (stenosis), 1 ileal-loop diversion (stenosis).

19 underwent internal urethrotomy or transurethral resection of the bladder neck. The largest group of the children, viz. 78 (i.e., 62%) were treated with reimplantation of the ureter by the Politano-Leadbetter technique. The Bischoff technique was used in only 2 cases. Finally, nephrectomy was performed in 2 children, and ileal-loop diversion in 1.

Antibiotics were not used prophylactically and were given postoperatively only in a few cases.

Operative Complications

These are shown in Table IV.

Table IV

Operative Complications encountered in 126 Children with Vesico-ureteral Reflux

Type of complication	No.	Treatment	No.
Death within first month	1	Pyelostomy	1
Hydronephrosis	4	Temporary pyelostomy	1
		Temporary ureteral tubulation	2
		Lysis of the ureter	1
Local wound infection	2	Incision	2
Wound disruption	1	Closure	1
Total	8	Total	8

Table V

Causes of Re-operation in the Treatment of 126 Children with 193 Renal Units with Vesicoureteral Reflux

Causes of re-operation	No. of renal units
Persistent reflux	12
Postoperative ureterovesical stenosis	3
Reflux and ureterovesical stenosis	1
Total	16

Table VI

Results of Treatment assessed by Micturating Cystography in 193 Renal Units

		Reflux after definitive treatment					
	Total No. of renal units	Eliminated		Diminished		Unchanged (No.)	Miscellaneous (No.)
		No.	%	No.	%		
Medical treatment only	23	12	52	1	–	4	6
Surgery on the urethra	52	30	57	12	23	10	0
Reimplantation of the ureter							
Leadbetter technique	110	95	86	11	10	0	4
Bischoff technique	3	1	–	0	–	2	0
Nephrectomy/ileal loop	5	–	–	–	–	–	5
Total	193	138	72	24	12	16	15

One child with urethral valves, left-sided grade III reflux and right-sided juxtavesical stenosis was treated with reimplantation of both ureters and removal of the urethral valves. After operation, acute pyelonephritis and sepsis developed, and in spite of pyelostomy and antibacterial therapy death occurred 3 weeks later. In 4 cases, hydronephrosis occurred postoperatively; it was treated with temporary pyelostomy in 1, temporary ureteral tubulation in 2, and lysis of the ureter in 1.

The patients were followed postoperatively with urography, micturating cysto-urethrography, blood chemistry and urine cultures at 3, 6 and 12 months, and then at 1-year intervals. The periods of observation range from 2 to 9 years.

Owing to unsatisfactory results, 16 children underwent re-operation. The causes of re-operation are shown in Table V. In most of the cases, repeat ureteral reimplantation was done; once in 11 children and twice in 1 child. Nephrectomy was performed in 1 patient, and ileal-loop diversion in 2 renal units (same patient).

Results

The results reported below are those obtained after definitive treatment, i.e., after primary operation and re-operation, if any. Table III is a survey of the results in all 126 patients. A more detailed, but largely unchanged picture appears from Table VI, in which the results are assessed by micturating cystography in all 193 renal units with a view to changes in vesico-ureteral reflux. Elimination of the reflux was obtained in 12 of 23 renal units (52%) in children who had received medical treatment only; in 30 of 52 renal units (57%) in which infravesical obstructions had been removed; and in 95 of 110 units (86%) in which reimplantation had been performed. In addition, reduction of the reflux was observed in 12 and 11 patients, respectively, in the second and third of these groups. Ileal-loop diversion was performed in 1 patient with 2 renal units, and 3 renal units were removed.

In Tables VII, VIII and IX the results are related to the grades of reflux. Most of the conservatively treated renal units were found in the group with grade I reflux. In nearly all cases (9 out of 10) the reflux ceased. The results after correction of infravesical obstruction and reimplantation are also better than in the groups with reflux of grades II and III. Thus, conservative treatment seems to be less effective in the group with grade II reflux, and it also seems to be more difficult to obtain normal urographic conditions. In the group with grade III reflux this situation is even

Table VII

Results of Treatment in 41 Renal Units with mild Vesico-ureteral Reflux (Grade I) (Renal Scarring in 2 Units (5%))

	No. of renal units	Postoperative micturating cystography	
		Reflux eliminated (No.)	Reflux unchanged (No.)
Conservative treatment	10	9	1
Surgery on the urethra	21	18	3
Reimplantation (Leadbetter)	10	10	0
Total (grade I)	41	37	4

	No dilatation (Pre- or postop.)	Pre-operative dilatation		Renal scarring without dilatation (Unchanged)
		Eliminated	Unchanged	
Postoperative IVP	38	2	0	1

Table VIII

Results of Treatment in 68 Renal Units with Moderate Vesico-ureteral Reflux (Grade II) (Renal Scarring in 15 Units (22%))

		Postoperative micturating cystography		
	No. of renal units	Reflux eliminated (No.)	Reflux diminished (No.)	Reflux unchanged (No.)
Conservative treatment	8	4	1	3
Surgery on the urethra	20	12	4	4
Reimplantation (Leadbetter)	38	37	0	1
Heminephrectomy	1	–	–	–
Urinary diversion	1	–	–	–
Total (grade II)	68	53	5	8

	No dilatation (Pre- or postop.)	Pre-operative dilatation		Renal scarring without dilatation (Unchanged)
		Eliminated or diminished	Unchanged	
Postoperative IVP	49	6	2	11

Table IX

Results of Treatment in 84 Renal Units with Severe Vesico-ureteral Reflux (Grade III) (Renal Scarring in 23 Units (28%))

		Postoperative micturating cystography			
	No. of renal units	Reflux eliminated (No.)	Reflux diminished (No.)	Reflux unchanged (No.)	Miscellaneous (No.)
Conservative treatment	5	–	–	1	4
Surgery on the urethra	4	–	4	–	–
Reimplantation					
Leadbetter technique	69	60	4	1	4
Bischoff technique	3	1	–	2	–
Nephrectomy	2	–	–	–	2
Urinary diversion	1	–	–	–	1
Total (Grade III)	84	61	8	4	11

	No dilatation (Pre-postop.)	Pre-operative dilatation				Renal scarring without dilatation (Unchanged)	Other findings
		Eliminated	Diminished	Unchanged	Worse		
Postoperative IVP	14	17	24	5	2	13	9

Table X

Results of Treatment in 193 Renal Units assessed by Intravenous Pyelography

	Renal Units	
	No.	%
No nephropathy or dilatation	101	52
Reflux nephropathy without dilatation, unchanged	25	13
Dilatation before treatment	58	30
Dilatation after treatment		
Eliminated	25	85
Diminished	24	
Unchanged	7	
Enhanced	2	
Other findings	9	5
Total	193	100

Table XI

Presenting Symptoms (A) in the Order of Decreasing Frequency and the Effect of Treatment (B) in 126 Children with Vesico-ureteral Reflux

A. Presenting symptoms			B. Symptoms after treatment		
	No.	%	Cured No.	Improved No.	Unchanged No.
Fever and flank pain	75	60	62	8	5
Recurrent cystitis	51	40	41	9	1
Enuresis	33	26	20	9	4
Failure to thrive	28	22	19	5	4
Abdominal colics	13	10	11	2	0
Total No. of symptoms	200	–	153	33	14
Total No. of patients	126	100	99 (79%)	19 (15%)	8 (6%)

more conspicuous. Only in 61 of 84 renal units (75%) was complete cessation of the reflux achieved. The pre-operative dilatation disappeared only in 17 of 48 units (35%); but it was reduced in another 24 units (50%), remained unchanged in about 10%, and became worse in 4%.

A survey of the results in the 193 renal units as assessed by intravenous pyelography is shown in Table X. Before treatment, normal urographic conditions were found in 101 of the 193 renal units (52%), and renal scars were present pre-operatively in 25 units (13%). The scarring was unchanged after operation. In 58 renal units (30%) the pre-treatment urograms showed dilatation; after operation, the dilatation had either disappeared or was reduced in 49 units (85%). Only in a small group (about 15%) was the dilatation unchanged or had increased.

The pre- and postoperative symptoms appear from Table XI. The clinical results are in agreement with the findings in micturating cysto-urethrography and intravenous urography. Of the children, 79% were free of symptoms after treatment. Failure to thrive, as a characteristic feature in children under 2 years of age, was superseded by normal growth in more than two-thirds of the cases. Episodes of pyelonephritis, characterised by fever and flank pain, did not occur in 62 of the 75 patients (82%) after operation. In view of the close relationship between dilatation

Table XII

Frequency of Bacteriuria before and after Treatment ($\geq 10^5$ col./ml) and Previous Antibacterial Therapy in 126 Children with Vesico-ureteral Reflux

Before treatment	No.	After treatment Bacteriuria Absent (No.)	 Present (No.)	 No information (No.)
Bacteriuria absent	6	5	1	–
Bacteriuria present	120	74	44	2
Total	126	79 (63%)	45 (36%)	2
No pre-operative antibacterial therapy	25			
Several courses of antibacterial therapy	86			
Long-term antibacterial therapy	12			
No information	3			

Table XIII

Patho-anatomical Findings of the Distal Ureter in 113 Reimplanted Ureters

Patho-anatomical findings	No.	%
Normal ureter	13	11
Slight oedema	2	1
Hypertrophy of muscle tissue	13	11
Chronic unspecific inflammation	26	24
Fibrosis and chronic inflammation	18	16
Slight fibrosis	29	26
Severe fibrosis	12	11
Total	113	100

of the upper urinary tract and the occurrence of acute pyelonephritis, there is also here good agreement between the radiographic and clinical findings.

Before treatment, significant bacteriuria was present in 120 of the 126 children in spite of long-term antibacterial therapy or several courses of antibiotics. Only 25 of the children had not received antibiotics before admission. The frequency of bacteriuria before and after treatment is shown in Table XII. It should be noted that in spite of the large number of successful reflux operations, sterile urine was achieved only in 63% of the children, while significant bacteriuria was still present in 36% after treatment.

Patho-anatomical Findings

In all cases of ureteral reimplantation, the distal part of the ureter was subjected to histological examination. The observations appear from Table XIII. The most frequent finding was fibrosis, which was present in 53% of the cases; in 16% it was associated with inflammatory changes.

Chronic inflammation was found in 41% of the ureters. Completely normal ureteral tissue was observed in 11%.

9 renal units were also studied histologically; 3 had been removed by nephrectomy and 6 were studied after autopsy. 7 renal units showed chronic pyelonephritic changes. In a patient who died while under conservative treatment, 1 unit showed severe acute pyelonephritis with abscess formation, while the unit on the other side revealed severe dysplasia without inflammatory changes.

Discussion

The follow-up examination of the 126 children with vesico-ureteral reflux showed that cessation of primary reflux was achieved in 86% of the renal units by Politano-Leadbetter reimplantation of the ureter—a result which is in good agreement with those previously reported. In renal units with reflux secondary to infravesical obstruction in which removal of the obstructive lesion was the only surgical intervention, the results were slightly less satisfactory, as reflux ceased only in 60% of the cases. The explanation may be that the obstruction had led to irreversible changes in the ureterovesical junction, so that removal of the obstruction was no longer sufficient at the time of operation. The treatment should possibly have been supplemented by ureteral reimplantation.

The conservatively treated group, which mainly comprised grade I reflux, showed the poorest results as far as the elimination of reflux was concerned, but the group is too small for definite conclusions.

In most cases (85%), successful operation led not only to the cessation of reflux, but also to a return to normal, or at least to improvement of the dilatation of the renal pelvis and ureter as assessed by intravenous urography—a fact to which great importance must be attributed in view of the close association between clinical pyelonephritis and urinary-tract stasis. In fact, not less than 82% of the patients who had previously had episodes of pyelonephritis experienced no further attacks, and another 10% showed considerable improvement. On the other hand, the frequency of the occurrence of significant bacteriuria did not decrease correspondingly. At the follow-up, 63% had sterile urine, whereas bacteriuria persisted in 36%. Several other studies point in the same direction (Williams, 1971; Ericsson, 1976; Fair and Govan, 1976). However, it seems as if bacteriuria is of less significance when the reflux has been eliminated, since the frequency of pyelonephritic attacks decreased.

Both this study and several others (Rolleston *et al.*, 1970; Govan *et al.*, 1974) reveal a correlation between the grade of reflux and the occurrence of "pyelonephritic" changes in the kidney, which, on intravenous urography, appears to be small with clubbed calyces and an irregular outline. In intravenous urography, it is difficult to distinguish these changes from renal dysplasia; this can be done only by a histological examination. In the present series, needle biopsy was not performed, but owing to the focal distribution of the lesions, this procedure would presumably only in a few cases have been able to reveal the true nature of the lesions. It should, however, be emphasised that of the renal units which were accessible to histological examination, 8 showed changes suggestive of chronic pyelonephritis, while only 1 unit revealed dysplasia without inflammatory changes.

Vesico-ureteral reflux may disappear spontaneously in many cases (Williams, 1971; Govan *et al.*, 1974). Thus, in about 700 children treated in the Department of Paediatric Surgery of the Karolinska Sjukhuset, Stockholm, the reflux disappeared spontaneously in more than 50%, remained unchanged in 35%, and aggravated in about 8% (Ericsson, 1976).

On the other hand, sufficient knowledge is scarcely available as to the risk of damage to the renal parenchyma in the presence of reflux which has been left untreated for a long period or been treated conservatively. Several investigators advocate conservative treatment even in the presence of severe reflux if only the urine is kept sterile (Williams, 1971; Govan *et al.*, 1974). However, it seems as if renal function can be severely impaired in children with grade III reflux, even when the urine is sterile (Aperia *et al.*, 1976). Owing to our limited knowledge of these problems, it is still impossible to give definite guide-lines on the treatment. If it be attempted to lay down indications for treatment, they should be roughly as follows:

1. In secondary reflux, demonstrable infravesical obstructions should invariably be removed.
2. In primary grade III reflux, reimplantation should be preferred, whether urinary-tract infection is present or not.
3. In primary reflux grade I or II, the treatment should be individualised. Conservative treatment should be preferred unless pyelonephritic episodes or subjective discomforts occur, or unless urinary-tract infection persists in spite of adequate long-term antibacterial therapy.

In the third of these groups, a prospective randomised study is urgently required—and will be ethically justified.

Summary

A total of 126 children with 193 refluxing renal units were treated for vesico-ureteral reflux during the period 1966-74. The grading of the cases into mild, moderate and severe reflux revealed renal scarring in 5, 22 and 28% of the three groups.

Conservative treatment was used in 10% of the patients, surgery on the urethra in 25%, and reimplantation of the ureter by the Politano-Leadbetter technique in the last two-thirds of the patients.

Reflux was eliminated in 50% of the renal units treated conservatively, in 60% of renal units treated with surgery on the urethra, and in 86% of units treated with reimplantation. The overall results seemed to be better in mild than in moderate or severe reflux.

The dilatation of the upper urinary tract returned to or approached normal in 85%. Of the children, 80% were without symptoms postoperatively, whereas urinary-tract infection persisted in 36%.

The value of the grading of reflux is emphasised, and indications for treatment are discussed.

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The Authors

B. E. Jakobsen, MD, DMS(Aarhus), Head of the Department of Surgery K (Urology), University Hospital, Aarhus, Denmark.

H. Genster, MD, Chief Surgeon, Lecturer.

S. Olesen, MC, Senior Urological Registrar, Lecturer.

E. Nygaard, MD, Senior Urological Registrar.

Correspondence to: Bent E. Jakobsen, Department of Surgery K (Urology), DK-8000 Aarhus, Denmark.

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Short Case Report

"Milk of Calcium" Syndrome in a Hydronephrotic Kidney due to Obstructing Stone

A 65-year-old male presented with a 5-month history of intermittent painless haematuria. Physical examination and blood analysis were normal. Urinalysis revealed haematuria with no leukocyturia. Urinary excretion of Ca-P-Uric Acid were normal. Erect plain abdominal X-ray showed a very enlarged left kidney with a triangulated stone and opaque fluid levels due to "milk of calcium" (fig.). IVP showed a normal right kidney and a grossly hydronephrotic left kidney with minimal excretion of contrast dye. The stone filled the renal pelvis causing partial obstruction; the renal parenchyma was extremely diminished. Nephrectomy was performed. Postoperative recovery was uneventful.

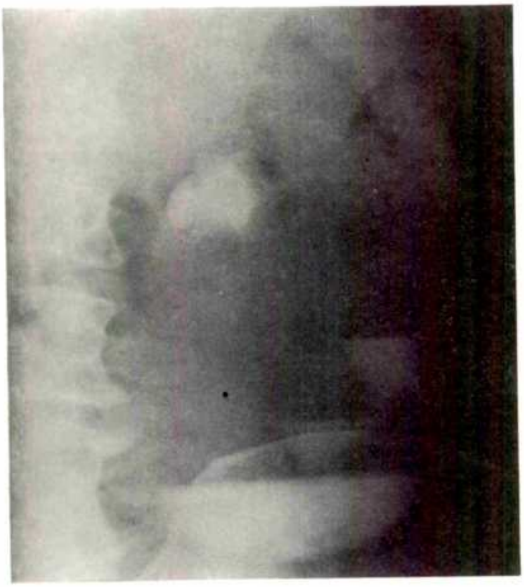

Fig. 1. Erect position plain film showing big triangulated stone and opaque fluid levels due to milk of calcium.

Pathologically the kidney consisted of cyst-like calyces lined by inflamed mucosa. Biochemically the stone consisted of calcium-oxalate and the fluid contained calcium-oxalate crystals.

Comment

The overall number of cases described with renal "milk of calcium" is small. 3 cases have been described in hydronephrotic kidneys and only 1 of these was due to an obstructing stone. We are communicating a second similar case. Symptomatology of the syndrome is not specific. Pathogenesis of the development of this special fluid is not clear but there are several theories, including urinary stasis with superimposed infection. The presence of an obstructing stone alone is not sufficient to explain this phenomenom. Obstructive hydronephrosis secondary to lithiasis is extremely common but "milk of calcium" is rare.

Santiago Richter, Michael Aharonheim and Leon Bechar
Department of Urology, Meir General Hospital, Kfar Saba, Israel

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Bladder Trauma in the Long-distance Runner: "10,000 Metres Haematuria"

N. J. BLACKLOCK
Royal Naval Hospital, Haslar, Gosport, Hants PO12 2AA

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Haematuria as distinct from haemoglobinuria features in sports traumatology but is overshadowed by muscle, tendon, joint and skeletal injuries. It is described in boxers, skiers, and footballers (Frey, 1969) and also occurs in runners, rugby players and Servicemen undergoing arduous physical training. Renal trauma and renal vascular spasm have been postulated as a cause (Frey, 1969) but underlying lesions such as hydronephrosis, renal cyst or tumour and renal stone require to be excluded where the haematuria is a recurrent symptom.

In a urological practice which comprises a proportion of young fit men involved in their Service duties in heavy physical exertion and also encouraged in sporting activities, haematuria in association with these has perhaps been more of a feature than in urological practice elsewhere. Each case has prompted urological evaluation and whilst a number have been found to have one or other of the renal lesions already mentioned the majority have shown no abnormality in the upper urinary tract. A characteristic of haematuria of upper urinary tract origin following physical exertion has been its tendency to be recurrent, generally slight in amount and a careful history has sometimes elicited loin pain on the affected side.

Patients

Of 18 in whom no upper tract lesion was identified 8 were found on cystoscopy to have bladder contusions. The uniformity of these and the similarity of the circumstances in each case have suggested a specific syndrome.

Cases have invariably been runners involved in distances of 10,000 metres or longer and the haematuria has been an occasional event. It has occurred at the first voiding of urine after the completion of the run and has been typically profuse, sometimes with the passage of small clots. It has usually been painless although dull, suprapubic discomfort has been described with some reference of pain to the tip of the penis. Subsequent specimens have either been only slightly tinged with blood or macroscopically clear. In all cases, the urine has been reported clear within 24 hours. Specific questions have failed to differentiate the circumstances of the run in which haematuria has occurred from those on the other occasions when it was not noted. Enquiry in this respect was made of the amount and time of the last drink and the time of the last voiding of urine beforehand and the bowel habit. From this there was the impression that the phenomenon was a random event whose occurrence could not be predicted.

The Bladder Lesion

The cystoscopic appearances have varied in degree according to the interval between the haematuria and the examination. Within 48 hours of the event localised contusions with loss of urothelium and fibrinous exudate have been found in characteristic sites within the bladder (Fig. 1). The inter-ureteric bar has been involved with its extension laterally overlying the intra-

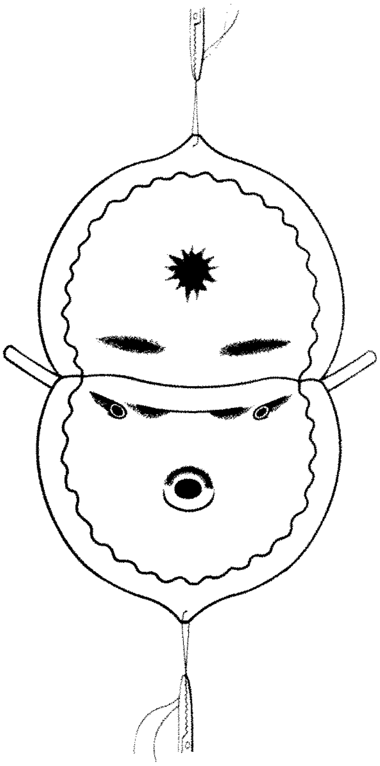

Fig. 1. Diagram of typical distribution of contusions within the bladder.

mural ureter on each side (Fig. 2). The posterior rim of the internal meatus has shown similar changes. The counterpart of these contusions has been noted on the lower posterior bladder wall and in most instances there has been a "mirror-image" of the lesions of the trigone (Fig. 3). The lower of the posterior wall lesions has usually been bilateral suggesting contact on each side between these and the most prominent parts of the inter-ureteric ridge. The upper posterior wall lesion has been the most pronounced and in one instance there was a gross contusion approximately 3 cm in diameter. The more discrete lesions in this situation have shown a radiate appearance (Fig. 4), suggesting that this part of the posterior wall has impinged on and been forced into the depression at the internal meatus.

Resolution of these lesions is rapid and mild hyperaemia has been the sole residual appearance a week after the event.

Comment

The appearances suggest that the mode of production of the injury is repeated impact of the flaccid posterior wall of the bladder against the bladder base. The base is altogether a thicker and more rigid structure since it comprises the trigone, the terminal ureters and the underlying prostate. It is relatively fixed because of the tethering caused by the insertion of the ureters on each side, the lateral vesical ligaments and the continuity in the region of the internal meatus with the prostate below. These trigonal features will be thrown into greater prominence by the contraction

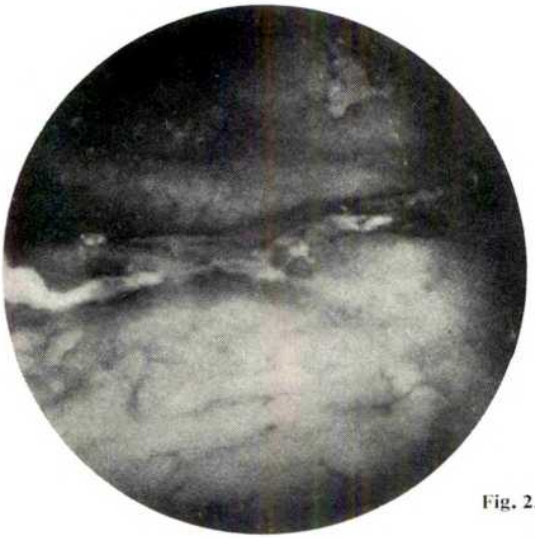

Fig. 2.

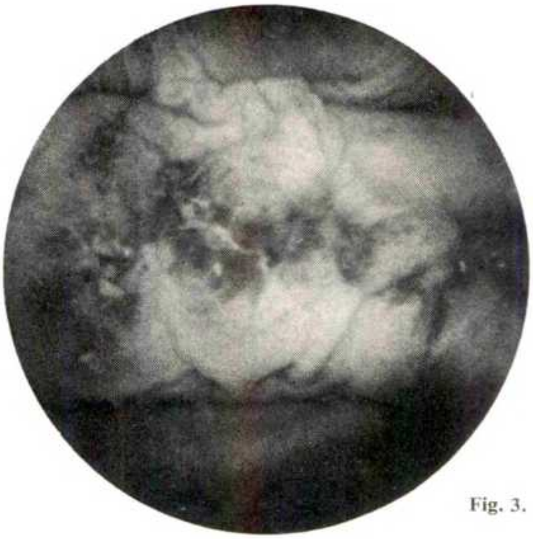

Fig. 3.

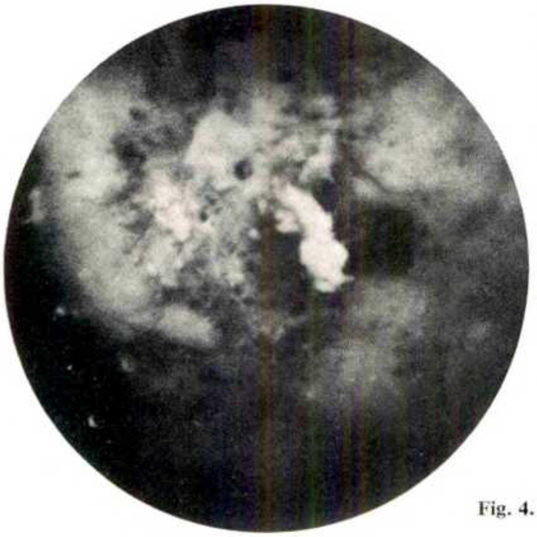

Fig. 4.

Fig. 2. Contusion with fibrinous exudate on inter-ureteric bar and extension on to prominence caused by intramural ureter.

Fig. 3. Linear contusion on fold of posterior bladder wall matching the contusion shown in Figure 2.

Fig. 4. Midline lesion on posterior bladder wall showing radiate ecchymoses, fibrinous exudate and contusion.

of the underlying pelvic floor musculature which is the constant accompaniment of exertional effort. Counter-force from momentary increase of intra-abdominal pressure in the same circumstances will force the surface of the posterior bladder wall into apposition with the trigone. Whilst each impact in itself is probably minor and relatively insignificant, with repetition of this in accompaniment of each stride during a long run, summation of effect to produce injury may be assumed (Fig. 5).

The suggestion of this mode of injury presumes that the bladder is either empty or nearly empty at the time to allow apposition of the surfaces. This assumption can also account for the inconsistency of occurrence of haematuria in the same individual since, when haematuria does not occur, the postulate is that there has been sufficient urine within the bladder to act as a hydrostatic cushion, preventing the apposition of the posterior bladder wall and the trigone.

The lesion is superficial and resolves spontaneously although giving rise to profuse haematuria

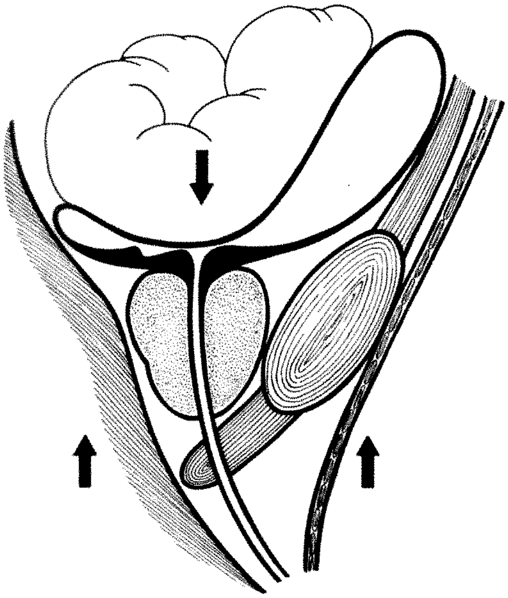

Fig. 5. Hemi-sectional diagram to show the forces presumed causal of the contusions.

at the time. Theoretically it should be avoidable by the intake of fluid before running or the omission of bladder emptying before the run commences. Neither of these measures is easily acceptable by the dedicated athlete for fear of interfering with his running performance.

Summary

Profuse, short-lived haematuria occurring as an occasional event in a number of long-distance runners has been found to originate from lesions in the bladder.

These lesions are either ecchymosis or frank contusions which have a typical distribution. They are sited on the inter-ureteric bar, the posterior half of the rim of the internal meatus and on the posterior bladder wall in which position there is "mirroring" of the trigonal lesions.

The possible mode of injury is discussed.

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The Author

N. J. Blacklock, OBE, FRCS, Surgeon Captain, RN, Consultant in Urology.

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The Concept and Measurement of Bladder Work

P. H. ABRAMS, R. SKIDMORE, A. C. POOLE and D. FOLLETT

Clinical Investigation Unit, Ham Green Hospital; Department of Urology, Bristol;
and Department of Medical Physics, Bristol General Hospital

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Urodynamic studies are becoming accepted as an important method of investigating patients with urinary tract disorders. The basis of these studies is the measurement of intravesical pressure during bladder filling and both pressure and urine flow rate during voiding. Such a pressure-flow analysis of micturition provides additional information to that obtained from radiological and endoscopic techniques. During voiding, the variables of pressure and flow are found in several combinations, for example, high pressure with low flow rate and high pressure with a high flow rate. In an attempt to compare those patients with different voiding patterns and to assess the degree of bladder outflow obstruction in these patients, the concept of urethral resistance was introduced (Claridge, 1964). This expression, urethral resistance, relates the maximum flow pressure (P) to the maximum urine flow rate (F) as P/F^2 (Smith, 1964). However, any derived expression is dependent on its variables and, whilst it is generally accepted that the maximum flow pressure is similar for different voided volumes, it is known that the maximum urine flow rate varies considerably for voided volumes of less than 150 ml (Von Garrelts, 1957) and is variable for greater volumes (Von Garrelts, 1957; Smith, 1964). An expression such as urethral resistance may also be criticised as it is measured at one point during micturition although the intravesical pressure and urine flow rate change continuously throughout voiding.

The concept of bladder work in urodynamics was introduced by Campbell (1965). He used bladder work during the interpretation of urodynamic data from children with lower urinary tract disorders and found these measurements valuable in differentiating between those children suffering from enuresis, reflux and bladder-neck obstruction.

The bladder volume, intravesical pressure and urine flow rate can be measured and recorded throughout bladder filling and emptying and, from these measurements, deductions can be made about the activity of the bladder and the degree of intravesical obstruction. If possible, a single expression should be derived from these measurements. That expression should be independent of the volume voided, should describe the whole act of micturition and should be straightforward in its derivation. Bladder work is presented as an expression that may meet these requirements.

In any physical system work is equal to force multiplied by distance. In the field of hydrodynamics this equation becomes: work = pressure × volume. If intravesical pressure and bladder volume are measured throughout bladder filling and emptying, a pressure volume loop is obtained (ACDEA in Fig. 1). The area within this loop, given by the integral PdV, represents the work done during voiding (W_{out}). However, the loop area represents only part of the total work done by the bladder during voiding: that part due to its contractile properties. The bladder also has viscoplastic-elastic properties (Alexander, 1973). By virtue of these latter properties a certain amount of energy is stored in the bladder wall during filling. This energy is proportional to the area ABCA which lies between the resting bladder pressure line AB and the inflow limits of the pressure volume loop AC and may be considered to equal the work stored (W_{in}). Thus, the total

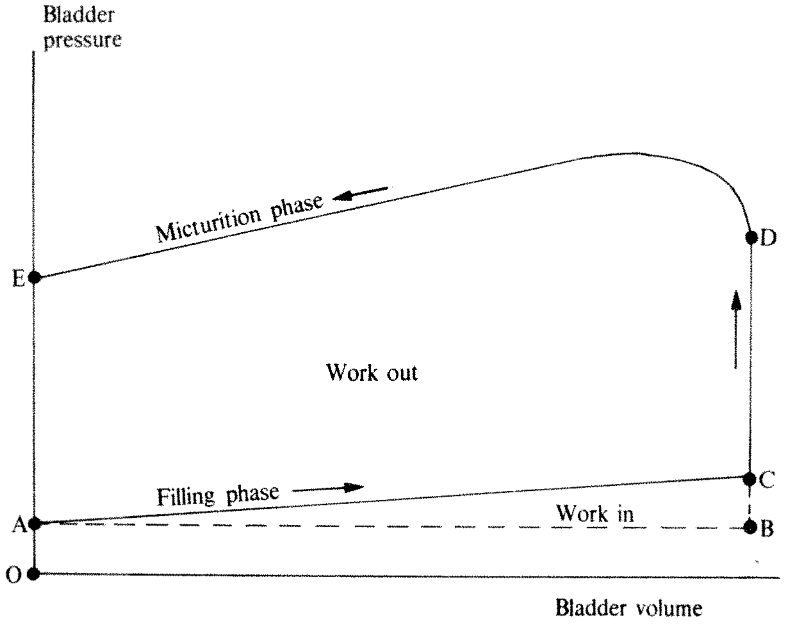

Fig. 1. Pressure volume loop showing areas of bladder work in and bladder work out.

work done during micturition (W_t), given by the area ABCDEA (Fig. 1) is given by: $W_t = W_{out} + W_{in}$.

Patients and Methods

The micturition data from 50 consecutive male patients seen at the Investigation Unit was analysed. The average age of these patients, 59·1 years, reflects the interest of the Unit in bladder outflow obstruction.

The basic urodynamic parameters of total bladder pressure (P), bladder volume (V) and urine flow rate were measured using an Elema Schonander EMT 34 pressure transducer and an EMT 434 uroflow transducer. An epidural catheter was used to measure bladder pressure and was passed per urethram with an 8 Fr. filling catheter. The bladder was then emptied to give zero volume. The saline source for the filling cystometrograms (at 37°C, 50 ml/min) was sited in an aluminium container which rested on the uroflow weight transducer. As the bladder filled and saline left the source, the weight on the transducer decreased. When the patient felt his bladder to be full the filling catheter was removed and the patient passed his urine into a bowl situated on the top of the saline source which in turn rested on the weight transducer. Hence, as the patient micturated the weight on the transducer increased. By a small modification to the amplifier of the uroflow transducer the mingograf (M81) recorder plotted an increasing volume during inflow and a decreasing volume during voiding. The urodynamic data passed from the mingograf recorder to a specially made computation unit and was then relayed to an XY plotter (Bryans 26000/A4).

Pressure volume loops (Fig. 1) were obtained by plotting total bladder pressure on the X axis of the XY recorder against bladder volume on the Y axis. Total work ($W_t = W_{in} + W_{out}$) was calculated and used for analysis. The areas of work in and work out were measured using simple analogue circuits (see below: Technical Methods).

Technical Methods

Work when related to pressure volume measurement is defined as Pdv with positive values indicating work done on the system, or work input, and negative values work done by the system, or work output. The above integral

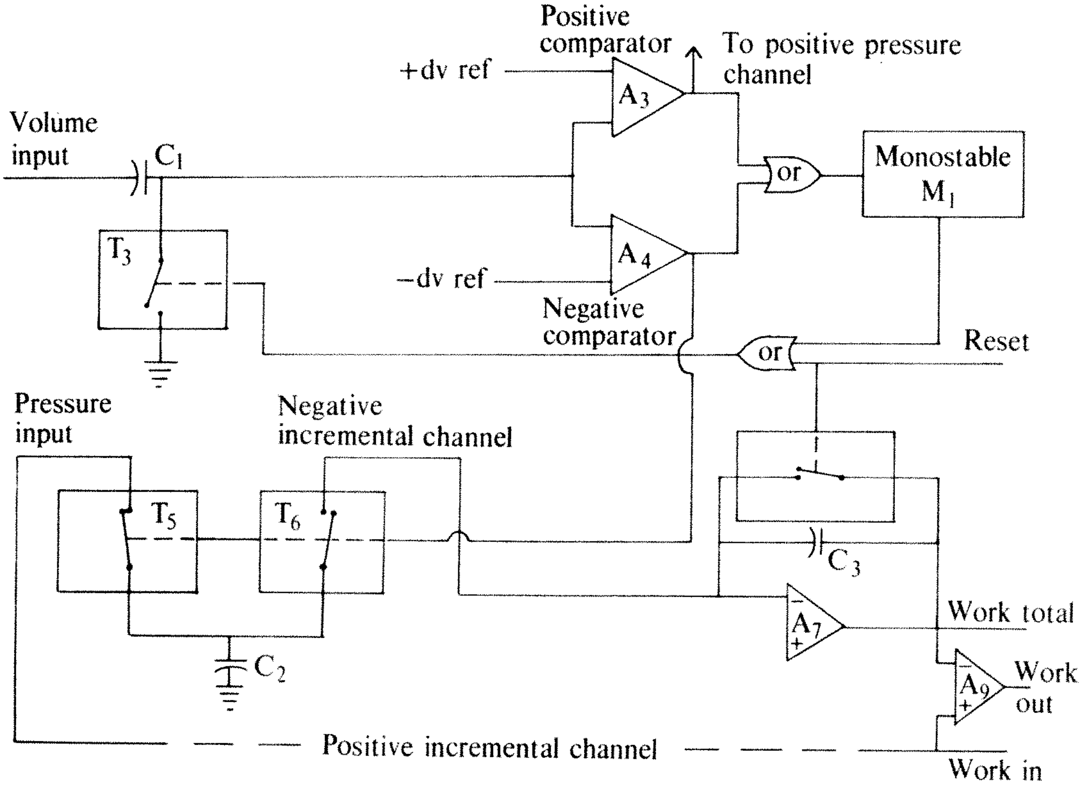

Fig. 2. Bladder work; block diagram.

can be approximated by the non-infinitesimal form $P_1 dv_1 + P_2 dv_2 \ldots + P_n dv_n$ where dv, etc. are now discrete increments in volume and P_1, etc. instantaneous values of pressure. If all the volume increments are equal, the expression for work involves only addition and multiplication by a constant, work $= dv(P_1 \ldots P_n)$. This is equivalent to finding the area under a graph by dividing it into equal width strips. For initial evaluation it was decided to perform the integration by implementation of this expression using simple analogue circuits.

Whenever the volume signal changes by a pre-set positive increment a charge proportional to the instantaneous pressure P is transferred to a tank capacitor whose final voltage thus represents the work input (W_{in}). For negative volume increments charge could be subtracted from the same capacitor, but instead it is added to a record tank capacitor whose final voltage represents total work (W_t). Work out (W_{out}) is found by subtraction of this voltage from the first.

Referring to the block diagram (Fig. 2), the right-hand side of C1 is originally at zero potential. If no charge can leak on or off C1 then the right-hand plate must vary in sympathy with any changes in the volume input potential. Considering the operation on negative or work-out increments of volume, if a negative excursion exceeding the negative reference on comparator A4 occurs the comparator is tripped. Field effect transistor switches T5 and T6 are operated and act as a changeover switch, disconnecting C2 from the pressure input and connecting it to the integrator composed of A7 and C3. Thus the charge on C2, representing the instantaneous pressure is transferred to the tank capacitor C3. After a slight delay, the monostable is fixed and resets the right-hand plate of C2 to zero potential via switch T3. A manual reset switch also discharges C2 and the tank capacitors to establish starting conditions.

In the pressure channels the switch potentials are arranged so that both polarities of pressure signals can be handled, enabling 4 quadrant operation to be achieved. To give sufficient time for transfer of charge in the pressure channels, a delay, before the comparators A3 or A4 are reset following tripping, is required. In the prototype

Table I

Basic Urodynamic Data

	Mean	Standard deviation
Peak urine flow rate (ml/sec)	12·3	6·9
Peak flow bladder pressure (mm. Hg)	85·5	25·0
Log urethral resistance	0·183	0·055
Volume (Vml)	226·0	134·0
Time (T sec)	50	32·0
Work in (W_{in}—joules)	0·20	0·19
Work out (W_{out}—joules)	1·60	0·78
Work total (W_t—joules)	1·80	0·78

Table II

Correlation between Urethral Resistance and Bladder Work Values

Work value	Correlation factor	Significance
Work in (W_{in})	−0·19	N.S.
Work out (W_{out})	+0·16	N.S.
Work total ($W_t = W_{in} + W_{out}$)	+0·11	N.S.
Work per unit volume $\frac{(W_t)}{(V)}$	+0·59	P<0·001
Rate of work $\frac{(W_t)}{(T)}$	−0·54	P<0·001
Rate of work per unit volume $\frac{(W_t)}{(TV)}$	+0·01	N.S.
Product of work per unit volume and time $\frac{(W_t \times T)}{(V)}$	+0·64	P<0·001
Square root of product of work per unit volume and time $\sqrt{\frac{W_t \times T}{V}}$	+0·70	P<0·001

there is an inherent delay of about 2 min around the loop which seems adequate, but, if necessary, further delay could be introduced. (Full electronic details may be obtained by writing to the authors.)

The *dv* reference potentials were set to make *dv* 10 mV and the pre-set pressure gain controls set to make 10 volts output correspond to 13·3 joules (100,000 mm Hg ml).

Probability has been calculated from the "*r*" value when the population coefficient is zero.

Results

The basic urodynamic data, the bladder work values and the correlations between the bladder work values and urethral resistance (P/F^2) are tabulated (Tables I and II). There was no correlation between the values of work in, work out and total work, and urethral resistance. Work per unit volume had a highly significant positive correlation with urethral resistance whilst there was a highly significant negative correlation between work per unit time and urethral resistance. Although there was a significant correlation with work per unit time, if this was related to volume

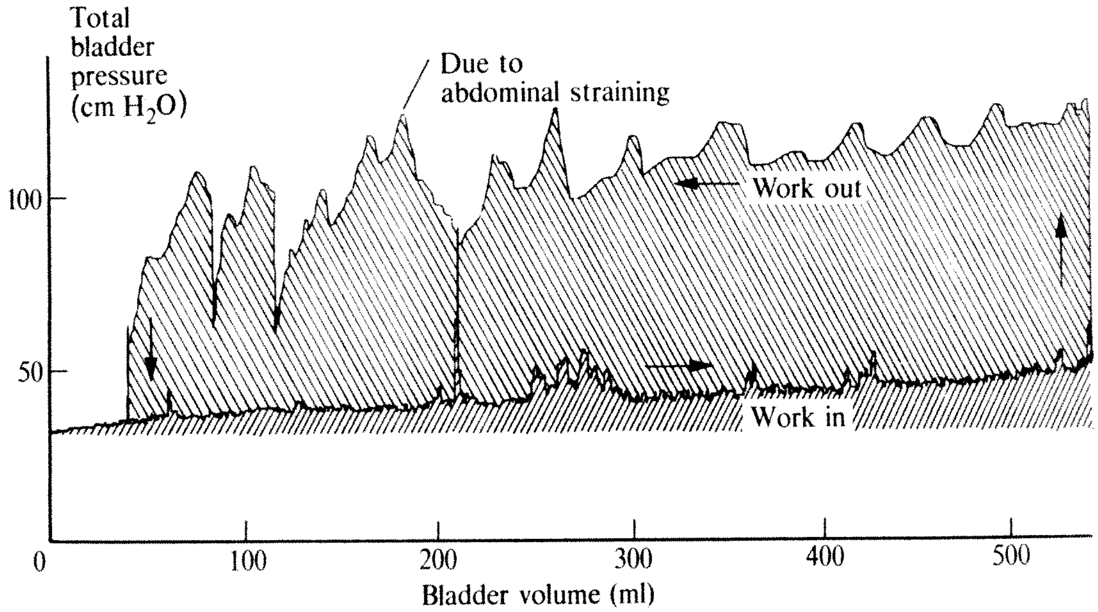

Fig. 3. Pressure volume loop showing areas of work in (W_{in}) and work out (W_{out}). Abdominal straining has been used to assist voiding and at the end of micturition there is a residual urine of 40 ml.

voided, i.e. the rate of work per unit volume, there was no correlation with urethral resistance.

The most significant correlation was that between urethral resistance and the product of work per unit volume and time, and the square root of this product.

Discussion

A method of measuring bladder work using simple analogue circuits has been described. The areas of work in and work out may also be measured manually by counting the squares on graph paper or by planimetry.

In this study total bladder pressure has been used for analysis although total bladder pressure does not discriminate between the pressure produced by detrusor muscle contraction and that produced by the contraction of the abdominal musculature. However, total bladder pressure has been used as, in the assessment of bladder outflow obstruction, both detrusor and abdominal pressure changes are important. Should a patient strain during micturition a characteristically wavy or spiky appearance is produced on the tracing (Fig. 3). If only the function of the bladder muscle is under investigation then the intrinsic bladder pressure should be used in bladder work calculations.

The bladder work values, work in, work out and total work showed no correlation with urethral resistance (UR) due to their correlation with the volume voided ($r = -0{\cdot}01$, $r = 0{\cdot}48$ and $r = 0{\cdot}47$ respectively). This was shown by the highly significant correlation between work per unit volume $\frac{(W_t)}{(V)}$ and UR. Although work per unit time $\frac{(W_t)}{(T)}$ showed a significant negative correlation with UR, it is interesting to note that the rate of work per unit volume $\frac{(W_t)}{(TV)}$ showed no such correlation. This lack of correlation suggests that bladder outflow obstruction results in an increase in work spread over a longer period of time and not in an increase in work rate or in power.

The XY plotter provided a satisfactory method of data presentation. The pressure-volume loop consists of an inflow cystometrogram and a voiding cystometrogram. The inflow cystometrogram may show the presence of bladder instability or abnormalities of bladder compliance, and after voiding a residual urine may be shown (Fig. 3). If a manual method of bladder work calculation is used the XY plotter may form the basis of a simplified recording system. In this system a pressure transducer and a weight transducer are necessary for the measurement of bladder pressure and bladder volume. Using suitable interface electronics the signals from these transducers may be fed into an XY plotter. By addition of a time marker on the volume axis a trace will be produced from which urine flow rate can be readily and accurately derived.

These results have demonstrated a relationship between bladder work and urethral resistance and justify further investigation into the role of bladder work measurement in the investigation of bladder pathophysiology.

Summary

The methodology for the calculation of bladder work from pressure volume traces has been described.

Bladder work values have been calculated from the urodynamic data of 50 male patients.

When bladder work values were related to the micturition time and the volume passed, a highly significant correlation was demonstrated with urethral resistance. Bladder work values may be a useful index in the diagnosis of bladder outflow obstruction.

We are grateful to the urologists of the Avon Clinical Area for allowing us to investigate patients under their care and to the Medical Research Council for financial support (Project Grant G974/135C). Our thanks also go to Mr Joe C. Smith for advice in the preparation of this manuscript and to Miss P. J. Abrams and Miss J. Foster for its typing. Our thanks also go to Mrs A. Morris of the Department of Community Health, University of Bristol, for her assistance in data analysis.

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The Authors

P. H. Abrams, FRCS, Research Registrar (now Surgical Registrar, Southmead General Hospital, Westbury-on-Trym).
R. Skidmore, BSc, Physicist.
A. C. Poole, Chief Technician.
D. Follett, BSc, Principal Physicist.

Correspondence to P. H. Abrams, Department of Surgery, Southmead General Hospital, Westbury-on-Trym, Bristol BS10 5 NB.

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Prostatic Obstruction in Sudan

A. KAMBAL

Urology Department, Khartoum North Hospital, Sudan

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Prostatic obstruction is a common disease in the Sudan. The purpose of this paper is to report on the frequency and regional variation in incidence of this urological condition.

Patients

The patients in this study are derived from the population of Central and Northern Sudan, who are the product of centuries of inter-marriage between Arab settlers and the indigenous African inhabitants. In this population, senile hypertrophy of the prostate is a common disease. The disease practically does not exist in Southern Sudan where the inhabitants are of pure African stock.

The patient is assessed in the usual way. Transvesical prostatectomy was performed in the majority of patients as a one-stage procedure.

Results

403 patients with prostatic obstruction requiring hospital admission were seen during the 7-year period 1969-75. They represent the patients seen by 1 of 3 urological units in the three-towns capital of the Sudan. Similar cases are admitted by general surgeons outside these units. Although all provinces have surgical units with qualified surgeons, patients tend to seek surgical treatment in the capital.

Pathology

Senile hypertrophy	395 patients
Carcinoma of prostate	8 patients

The 8 patients with prostatic carcinoma all had manifest carcinoma of the prostate proved by transrectal biopsy.

Residence and Ethnic Origin

Senile hypertrophy:	
Central and Northern Sudan	395 patients
Southern Sudan	Nil
Carcinoma of the prostate:	
Central and Northern Sudan	6 patients
Southern Sudan	2 patients

Nevertheless, 6 patients with senile hypertrophy were of purely African (Negro) origin. These belonged to various groups of pure Africans who have been living in Central and Northern Sudan for more than 100 years.

Age

Mean age	66·7 years
Range	42-105 years

Presentation

Acute retention of urine	76%
Chronic retention with renal failure	6·9%
Admission from waiting list	17·1%

Treatment and Outcome

Died before operation	19 patients
Unfit for operation	9 patients
Prostatectomy	367 patients
Postoperative deaths	11 (3%) patients

Histopathology of Removed Prostates

All prostates removed were sent for histopathological examination; pathological records were available for only 264 patients. The results were as follows:

Benign prostates with no evidence of malignancy	248
Adenocarcinoma of the prostate	16 (6·45%)

The latter were all reported as either well or moderately differentiated. There was no correlation between difficulty of enucleation and incidence of malignant change.

Discussion

During the 7-year period 1969-75, 403 patients with prostatic obstruction were admitted to this urological unit. This represents 69·6 per 10,000 total admission to Khartoum North General Hospital. Of these patients, 395 had senile hypertrophy of the prostate. Many more patients with mild symptoms were managed as out-patients and are not included in these figures.

Houston (1968) described 200 Central African Bantus with prostatic obstruction seen in 1 hospital in 4 years and reported an incidence of 50 admissions with prostatic obstruction per 15,000 total hospital admissions. Of these 200 cases, 148 had senile hypertrophy and 52 had carcinoma of the prostate.

Amaku, Da Rocha-Afodu and Elebute (1971) reported on 114 patients with prostatic obstruction seen during the 5 years (1963-67) in Lagos, Nigeria; an incidence of 134 per 10,000 adult male admissions. Of these, 75 patients had senile hypertrophy and 15 had carcinoma of the prostate.

It is often assumed that senile hypertrophy of the prostate is uncommon among Africans. The above data indicate that this assumption needs certain qualifications.

In Sudan, although senile hypertrophy of the prostate is common in the northern two-thirds of the country, it must be very rare in the south. This is borne out by the experience of surgeons and doctors who have worked in the south. The Southern Sudan has a population of about 3 millions. 3 major hospitals and 13 district hospitals are distributed throughout the region. It has been seen that 76% of our patients presented with acute retention of urine. Such a distressing presentation could not have escaped the notice of doctors working in the south had prostatic obstruction existed to any significant extent. In this series, not a single patient with senile hypertrophy came from Southern Sudan. However, 6 patients with senile hypertrophy were derived from a small group of pure Africans who have been living in Northern Sudan for a long time, probably over 100 years. Although this is a small number, it probably indicates that the difference in susceptibility to develop senile hypertrophy of the prostate between inhabitants of Northern Sudan (of Afro-Arab stock) and those of the south (pure Africans) is not due to genetic factors. This is borne out by the relative frequency of senile hypertrophy of the prostate reported in the Bantu of Central Africa (Houston, 1968) and in Nigerians (Amaku *et al.*, 1971) both of whom are of pure African stock. Factors relating to diet and sexual habits are more likely to explain the different incidence in the 2 parts of the country. Other so-called diseases of civilisation, such as diabetes

Table I

Incidence of Carcinoma of the Prostate in Africans as a percentage of all cases of prostatic obstruction

Author	Locality	Senile prostate (no. of cases)	Manifest carcinoma of prostate (no. of cases)	Carcinoma as % of the total no.
Movas (1966)	South Africa	73	57	44
Houston (1968)	Central Africa	148	52	26
Amaku *et al.* (1971)	Nigeria	75	15	16·6
Present work	Sudan	395	8	2

mellitus, coronary heart disease, gall stones and peptic ulceration which are frequently met with in Northern Sudan, are very rare in the south.

Only 8 out of 403 patients were found to have manifest carcinoma of the prostate, an incidence of approximately 2%. This is a very low incidence compared to that reported from other African countries (Table I). 2 of these 8 patients were southerners living in the south.

Carcinoma was discovered in 16 out of 284 enucleated prostates subjected for histopathological examination; an incidence of 6·5%. This is comparable to the findings in Nigerians, 5·1% (Amaku *et al.*, 1971) and Central African Bantus, 7·5% (Houston, 1968).

The age at which manifest carcinoma of the prostate was diagnosed was not different from that for senile hypertrophy. It cannot, therefore, be assumed that senile hypertrophy of the prostate is uncommon in Southern Sudan, because patients do not live long enough.

Summary

Prostatic obstruction is not uncommon among Africans.

Senile hypertrophy of the prostate is a common condition in Northern Sudan, while it is rare in the south. This difference in incidence is probably due to environmental rather than genetic factors.

Carcinoma of the prostate exists in both regions.

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The Author

A. Kambal, MS, FRCS, Consultant Urological Surgeon.

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Short Case Report

Gumma of the Testis

Gumma of the testis is extremely rare although that organ is particularly susceptible to syphilitic infection (Herman and Klauder, 1920). We report here the first case of testicular gumma seen at the University Hospital of the West Indies despite the high incidence of syphilis in Jamaica.

Case Report

A 59-year-old negro man presented with a 6-month history of a painful swelling and dragging sensation of the right side of the scrotum. On examination, the right testis was enlarged and felt hard with a bosselated upper end. It was tender on palpation. The spermatic cord was slightly thickened. The VDRL test was reactive 1 : 128. The gonococcal complement fixation test was positive.

At operation, the enlarged right testis was replaced by a hard mass, and it was excised after ligation of the spermatic cord at the deep inguinal ring. The left testis appeared normal. He was discharged from hospital on a 10-day course of long-acting penicillin.

Pathological examination showed a solid mass 9 × 7 × 5 cm. The cut surface was soft, pale yellow and gray, with a surrounding rim of very firm white scar tissue (Fig. 1). Microscopically, there was extensive gummatous necrosis with a surrounding area of proliferating fibroblasts, collagen, endarteritis obliterans, dense non-specific inflammatory cellular infiltration with mainly plasma cells and a granulomatous reaction with Langhans and foreign-body type giant cells. No preserved seminiferous tubules were present. The periphery of the mass showed chronic inflammatory cells in and around nerves (Fig. 2). Stains for spirochaetes and acid-fast bacilli were negative.

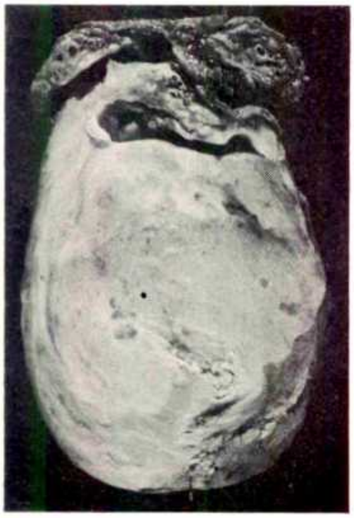

Fig. 1

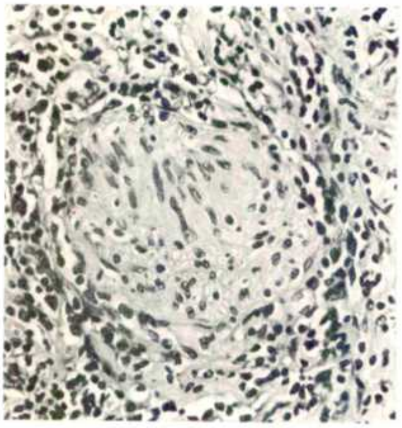

Fig. 2

Comment

Testicular gumma characteristically lacks sensation but pain may be produced by stretching of the spermatic cord or may be due to an associated hydrocele (Herman and Klauder, 1920). There was no hydrocele in our patient but he experienced pain when pressure was exerted on the testis. This was probably due to inflammatory infiltration of nerves at the periphery. The clinical differentiation between gumma and neoplasm of the testis is extremely difficult. However, the surgeon is justified in making a diagnosis of neoplasm rather than gumma even if serological tests for syphilis are positive (Blandy, Hope-Stone and Dayan, 1970).

V. Persaud and A. Rao

Departments of Pathology and Surgery, University of the West Indies, Kingston 7, Jamaica

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The Effect of Frusemide used for Post-prostatectomy Irrigation on Total Body Potassium

ANTHONY GOODE, T. HAWKINS, J. G. W. FEGGETTER

Department of Surgery, Hammersmith Hospital and the Royal Postgraduate Medical School, London W12;
Regional Medical Physics Department, Newcastle upon Tyne;
University Department of Surgery, Newcastle upon Tyne

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The use of diuretics in the postoperative management of the prostatectomy patient is well established. Urea and Mannitol solutions have been used most frequently until the advent of more powerful diuretics such as frusemide (Lasix). Mihailides and Amsler (1966) have described a regime of postoperative irrigation using frusemide, and this method has been further modified by Essenhigh and Eustace (1969) who have propounded that the regime limits blood clot formation, is physiologically a more attractive method of postoperative irrigation than conventional irrigation, and requires minimal interference with the catheter. Excellent results have generally been achieved using the technique. However, Rabelo *et al.* (1962) have pointed out that when Mannitol is used as a diuretic agent it is associated with a marked loss of potassium which may be of serious consequence to the patient. The study presented here was undertaken to examine the use of frusemide in the postoperative period and more specifically its effect upon the patient's total body potassium.

Material and Methods

A total of 20 patients requiring prostatectomy were admitted to the trial. The patients were free from associated cardiac or renal disease, were in normal acid base balance and were not taking diuretics.

Total body potassium determinations were made using a whole-body monitor of the shadow shield type (Warner and Oliver, 1966) with 2 sodium iodide detectors placed 1 above and 1 below the patient and shielded by 14 tons of pre-nuclear age battleship steel. A small and constant fraction (0·0, 12%) of all potassium is the naturally occurring radioactive nuclide potassium-40 which emits 1·46 MeV gamma rays. The radiation emitted from the body may be directly observed using a whole-body monitor, a highly sensitive radiation detector system. The total body potassium content (TBK) is obtained from:

$$\text{TBK} = \frac{\text{Net cpm from subject K40 content}}{\text{Net cpm/g from standard K40 mass}} \times F$$

Where $F = (1131{\cdot}4 + 5{\cdot}29 \times (W-70) + 2{\cdot}49 \times (H-170) \times 10^{-3}$; W = subject's weight in kilograms, H = subjects height in centimetres.

The calibration of the monitor to allow for differences in body build has been previously described (Hawkins and Goode, 1976). Thus using an appropriate calibration factor (F) for each individual, the counting rate observed by the monitor is related to the potassium status. The method allows rapid, serial, non-invasive estimations of the total body potassium. Wherever possible the patients were measured on 2 successive days before and twice after prostatectomy. In several patients a total of only 3 measurements could be made and a suitable weighting factor has been applied to the data in such cases. Thus if $n1$ and $n2$ are the number of potassium determinations made pre- and postoperatively, the relevant weighting factor is $(n1 \times n2)/(n1+n2)$ applied to the observed change. In all cases the "weight" took the values of 1 or 2/3.

This was a double blind trial, patients being randomly allocated to their group after surgery by opening a sealed envelope. The investigators did not know into which category a patient had been placed until the results were calculated at the end of the trial. Those patients on irrigation were managed by the nursing staff according to standard practice, the rate being that which kept the urine outflow pink to clear. The patients in the diuretic group were given 1 litre of fluid intra-

Table I

Frusemide group

Patient	Age (years)	Operation	K+ before (mmol K+)	K+ after (mmol K+)	Weighting	Weighted mean change (mmol K+)
G. E. K.	69	RPP	3423	3285	1	−138
R. G.	72	TUR	3346	3415	2/3	+ 46
H. S.	75	TUR	3315	3087	1	−228
W. F.	64	TUR	2756	2492	2/3	−177
W. M.	56	TUR	3826	4033	2/3	+138
W. G.	69	RPP	2964	3079	2/3	+ 77
T. H. L.	67	RPP	2831	2741	2/3	− 59
G. G. F.	58	TUR	4013	3854	2/3	−106
T. B.	58	TUR	3144	3128	2/3	− 10
J. C.	66	RPP	3913	3459	2/3	−302
					Weighted mean change	−104

RPP = Retropubic prostatectomy. TUR = Transurethral prostatectomy.

venously in theatre at a rate which as far as possible allowed completed administration before frusemide was given. In all, each patient was given 200 mg of lasix in the next 15 hours together with intravenous fluid at a rate equal to the urine output plus 500 ml. Potassium supplements were given to the group receiving lasix as slow-K 600 mg T.D.S. In both groups 6 patients underwent a transurethral prostatectomy and 4 underwent a Millin's prostatectomy.

Results

The results of the preoperative and postoperative potassium values and the weighted change in mmol for each patient in the 2 groups are shown in Tables I and II.

The standard deviation of ±100 mmol K estimated from the data did not differ significantly from the value obtained previously in the calibration of the monitor. Those patients showing an apparent increase in potassium are thus within the experimental errors of the technique.

Analysis of the data showed a small net loss of potassium in both groups and that the loss in those given frusemide with potassium supplement was greater than in the patients with irrigation. However, the difference was not statistically significant using the student test for independent data (t = 2·04, 0·1 > P > 0·05).

Discussion

Most of the potassium in the body lies principally within the cells of the lean body mass, the body fat being virtually potassium free. Serum and extracellular fluid potassium accounts for about only 3% of the total body potassium and it is perhaps not too surprising that changes in serum potassium may often fail to reflect changes in total body potassium (Flear, Cooke and Quinton, 1957, Healey *et al.*, 1970). A decrease in total body potassium may follow from several causes, though in broad terms it is due to either cellular loss of lean tissues or cellular depletion of potassium without marked loss of lean tissue. Changes in acid base balance towards acidosis have a noticeable depleting effect upon cellular K±. Walsh *et al.* (1974) showed that uncontrolled diabetics had cellular potassium loss. Boddy *et al.* (1975) showed a normal potassium concentration in lean tissue in patients with uretero-sigmoid anastomoses which may have been consequent upon the abolition of hyperchloraemic acidosis by long-term alkali therapy. The decreased

Table II

Irrigation Group

Patient	Age (years)	Operation	K^+ before (mmol K^+)	K^+ after (mmol K^+)	Weighting	Weighted mean change (mmol K^+)
N. E.	61	TUR	2905	3031	1	+126
G. B.	65	RPP	2831	2985	1	+154
C. W.	69	RPP	3259	3179	1	−80
T. S.	66	TUR	3744	3687	2/3	−38
W. K.	65	TUR	3095	2997	2/3	−64
E. H.	59	TUR	3672	3595	2/3	−51
A. M. G.	66	RPP	3000	3077	2/3	+51
J. M.	66	TUR	2677	2528	1	−149
F. S.	73	TUR	2359	2385	1	+24
R. G. A.	60	RPP	3479	3113	2/3	−243
					Weighted mean change	−32

RPP = Retropubic prostatectomy. TUR = Transurethral prostatectomy.

potassium levels observed by Bland *et al.* (1966) in muscular dystrophy patients were interpreted as the result of lost muscle mass rather than an altered intracellular potassium concentration.

There has been some disagreement over the effect of diuretic therapy upon intracellular and total body potassium levels. Edmonds and Jasani (1972) reported a significant decrease in total body potassium over a period of 1 year in hypertensive patients treated with diuretics. The results were, however, confused by the fact that other drugs were also being given with some patients taking potassium supplements. The decrease was not progressive but the total body potassium stabilised at a new level, not markedly below the initial value despite continued diuretic therapy. Dargie *et al.* (1974) investigated hypertensive patients with normal renal function who received 40 mg of frusemide per day without potassium supplements and found no significant fall in total body potassium after 1 year. Graybiel and Sode (1971) noted a fall in serum potassium but not total body potassium after 10 months in 12 patients taking 50 mg of hydrochlorathiazide daily and Wilkinson *et al.* (1975) found a non-significant decrease in total body potassium after 1 year in subjects taking 10 mg of bendrofluazide daily.

In the patients studied a loss of total body potassium could be expected as a result of loss of lean tissue from the obligatory metabolic response to trauma seen in the immediate postoperative period and a small loss reflecting a minimal degree of cellular depletion from acid bases changes in the postoperative period. In the frusemide group, if the diuretic was a potent cause of intracellular potassium depletion, a further significant loss might additionally be expected. The results clearly show that frusemide with a small potassium supplement used in the prostatectomy patient as a postoperative method of irrigation is not associated with significant potassium loss in marked contrast to the use of Mannitol. Consequently, it would seem that frusemide can be used with safety as described by Essenhigh:

> At operation 1 litre of fluid (500 ml of 4·8% dextrose in 0·18% saline and 500 ml of 5% dextrose) is given intravenously at a rate which allows its administration to be completed before frusemide is given, and usually before any blood transfusion which may be required is begun. Frusemide in an initial dose of 80 mg is injected as the bladder or prostatic capsule is being sutured or 10 min before the end of a transurethral resection. Free bladder drainage is maintained postoperatively via a urethral catheter connected to a standard plastic urine bag. Diuresis is usually evident at the conclusion of the operation. Intravenous saline or dextrose is given at a sufficient rate to match the urine output and to keep about 500 ml ahead of the flow of urine. Further injections of frusemide are given (either 80 mg or 40 mg) intramuscularly if the bleeding appears to increase postoperatively or if there is any suggestion that clot retention might become possible on account of an inadequate diuresis (<200 ml/hour)

in the presence of a heavily blood-stained urine. Blood is given as required. The intravenous transfusion is discontinued after 24 hours or earlier if the danger of clot retention is considered to have passed. Oral frusemide 40 mg and slow K 600 mg are administered thrice daily (to maintain a good urine flow). They are discontinued when the catheter is removed on the 3rd day.

There was no correlation between potassium loss and the type of operation or blood transfusion after surgery.

Summary

The effects of 2 techniques of bladder irrigation on total body potassium have been compared. The results show that a net decrease was associated with both methods. This was marginally greater ($0{\cdot}1 > P > 0{\cdot}05$) in the group which underwent a forced diuresis using frusemide with a fluid load. This group received some potassium supplements without which it is possible that the decrease would have been greater.

It is concluded that this regime cannot be overtly criticised for its potential loss of potassium.

We are most grateful to Mr W. K. Yeates and Mr D. M. Essenhigh for allowing us to study patients under their care and their help and encouragement during this study. We are further indebted to Dr M. J. Day for statistical advice and the staff of the Isotope Laboratory for technical assistance.

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The Authors

Anthony Goode, FRCS, Senior Registrar, Department of Surgery, Royal Postgraduate Medical School, London.

T. Hawkins, BSc, Senior Physicist, Regional Medical Physics Department, Newcastle General Hospital, Newcastle upon Tyne.

J. G. W. Feggetter, FRCS, Senior Registrar, University Department of Surgery, Royal Victoria Infirmary, Newcastle upon Tyne.

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Cinoxacin Concentrations in Plasma, Urine and Prostatic Tissue after Oral Administration to Man

R. A. P. BURT, T. MORGAN, J. P. PAYNE, R. M. BONNER

Lilly Research Centre Ltd., Erl Wood Manor, Windlesham, Surrey and
St Peter's Hospital, Henrietta Street, London WC2

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Cinoxacin is a synthetic compound which has cinnoline as the basic ring structure and an antibacterial spectrum similar to nalidixic acid and oxolinic acid. Its antibacterial activity against those Gram-negative organisms most frequently isolated in urinary tract infections has been studied in the laboratory by Giamarellou and Jackson (1975), Kurtz and Turck (1975) and Lumish and Norden (1975).

Studies of experimental pyelonephritis in rats (Holmes, Ensminger and Gordee, 1974) have shown that cinoxacin was considerably more effective than either nalidixic acid or oxolinic acid when the 3 drugs were compared at an oral dose of 3 mg/kg. Over a 12-hour period cinoxacin concentration in the urine was 3 times greater than the concentrations of the other 2 compounds.

Although the antibacterial activity of cinoxacin and nalidixic acid is similar, *in-vitro* the activity of cinoxacin is only reduced by 16% in the presence of human serum as compared with the 70% reduction in the case of nalidixic acid (Wick *et al.*, 1973). Studies by Panwalker, Giamarellou and Jackson (1976) have confirmed the efficacy of cinoxacin in the treatment of urinary tract infections in man.

Further preliminary studies in man showed that administration of cinoxacin every 12 hours produced urine concentrations which were greater than the minimum inhibitory concentration (MIC) of most organisms commonly causing urinary tract infection (Black, Brier and Wolny, 1975) and that the compound was predominantly excreted in the urine without being metabolised (Wolen *et al.*, 1975).

The present study was undertaken to measure the concentration in prostatic tissue obtained during transurethral prostatectomy, after the patients had received 4 oral doses of the drug, 500 mg given at 12-hour intervals. The protocol for this study was approved by the St Peter's Hospitals' Ethical Committee.

Patients and Method

Patients: 8 male patients in the age range 52-68 years, who had been admitted for transurethral prostatectomy were studied. All the patients had normal serum creatinine levels but 2 patients had slightly elevated blood urea levels: none of the patients had urinary tract infection as shown by routine microbiological examination of the urine on admission.

Patient Consent: The nature and purpose of the study was explained to each patient by different investigators on 2 occasions, firstly before the original dose of cinoxacin was given and secondly the next day before the first sample of venous blood was taken. Of the patients initially approached only 1 declined to take part.

Method: On the evening of admission each patient swallowed a capsule containing 500 mg cinoxacin. The next morning, approximately 12 hours after this dose and before breakfast, each

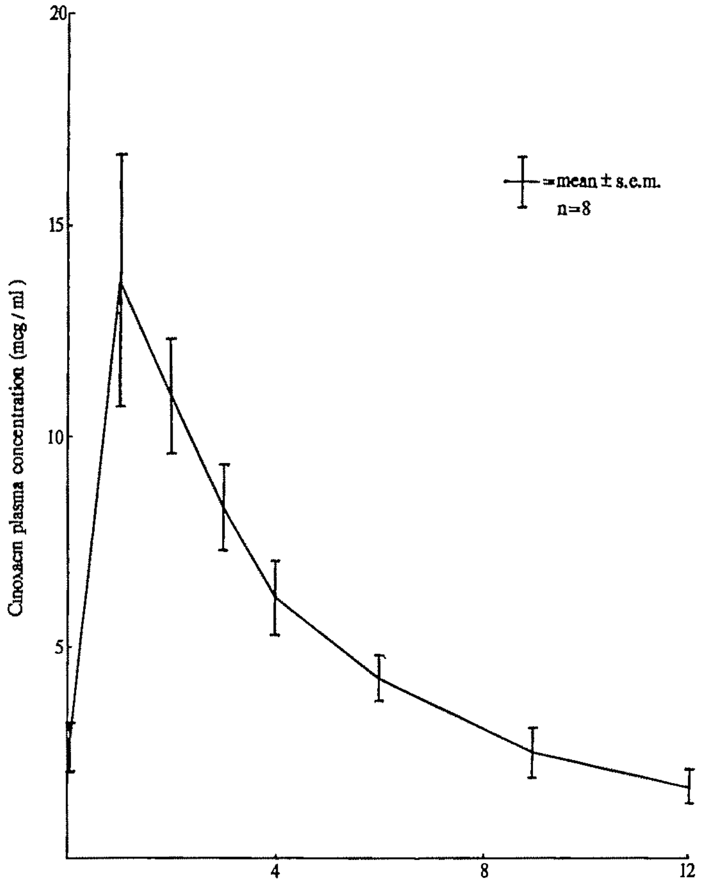

Fig. 1

patient emptied his bladder and the first venous blood sample was withdrawn through an indwelling cannula. The second capsule of cinoxacin was given with a glass of water immediately thereafter. Further samples of venous blood were collected at intervals for the ensuing 12 hours. The patients were given the normal hospital breakfast 30-60 min after dosing and other meals were taken at the usual times for the rest of the day.

Each patient received further doses of cinoxacin 500 mg in the evening after the last blood and urine sample had been obtained, and again the next morning together with 10 mg diazepam orally as pre-medication.

Anaesthesia was induced with althesin or thiopentone (see laboratory analysis) and suxamethonium was given to assist intubation: thereafter anaesthesia was maintained with halothane and oxygen. Samples of prostatic tissue were obtained during transurethral prostatectomy, and a sample of venous blood was taken at the same time.

Renal tissue: 1 male patient, who was admitted for partial nephrectomy, also agreed to take part in the study. Because this patient was receiving rifampicin and isoniazid for the treatment of renal tuberculosis, he was given only a single dose of 500 mg cinoxacin at the same time as his pre-anaesthetic medication.

Preparation of Samples

Venous blood was collected into lithium heparin tubes and centrifuged: the plasma was withdrawn into plain glass tubes and stored in a refrigerator until all the samples from that patient could be frozen. Aliquots of urine were similarly stored in plain glass tubes in the refrigerator until they could be frozen. 4 samples were lost because of breakage of the tubes.

As soon as the tissue was taken, it was rinsed in normal saline to eliminate contamination by blood and urine, blotted, placed in a plain glass tube and frozen with the other samples.

Laboratory Analysis

Cinoxacin concentrations were measured by fluorometric analysis using an Aminco Bowman spectrophotofluorometer (excitation 356 nm/emission 445 nm). Although fluorometric analysis is a non-specific method of measurement, the extraction procedure favours the separation of the parent drug from minor metabolites. Therefore the measurements of urine concentration essentially represent the levels of unchanged cinoxacin. The plasma, urine or homogenised tissue samples were made acid and cinoxacin extracted into an organic solvent: the drug was then back extracted into an alkaline buffer. The tissue extract required an additional extraction to reduce interference from biological contamination. The limit of sensitivity of this assay was approximately 0·2 mcg/ml.

In addition to the standards, blank samples of plasma, urine and prostatic tissue from untreated patients were carried through each assay. Relative concentrations of the drug were estimated by comparison with the standards after the respective blank values were subtracted. The other drugs that the patients received before or during the study were checked for interference by preparation of standard solutions of the drug which were then submitted to the extraction and estimation procedure. Only thiopentone was extractable and had a fluorescence spectrum similar to cinoxacin (excitation 315 nm/emission 513 nm); because of the small cross-over of the spectrum (< 10 %) and the low concentration of thiopentone in whole blood (< 2 mcg/ml), it was considered that this did not constitute any major interference to the assay of cinoxacin. However, as soon as the possible interference was known, *i.e.* after the samples from the first patient had been analysed, it was decided for all subsequent anaesthetic inductions to use althesin, which did not interfere with the cinoxacin assay.

Table I

Table shows the Patients' Age, Body Weight, Blood Urea, Serum Creatinine and Cinoxacin Plasma Levels

Patient	Age (yrs)	Body weight (kg)	Blood urea mmol/l Normal range	Serum creat. mmol/l	Plasma levels of cinoxacin; time (h) after administration							
			1·5-7·5	0 05-0·13	0	1	2	3	4	6	9	12
W. P.	59	60	5·7	0·10	2·9	18·8	12·6	7·2	4·4	3·3	1·1	0·7
J. J.	66	76	5·0	0·09	2·0	22·0	12·5	7·9	5 0	2·2	1·0	0·7
I. C.	61	68·5	8·6	0·09	4 3	27·3	16·8	12·5	9·5	3·5	1·8	1·1
P. P.	64	72	7 2	0·11	3 7	18 0	16 0	13·7	10·9	7·7	5·9	3·3
C. E.	58	70	5·2	0·10	1·0	5·2	6·4	6·2	4·8	4·3	1·8	1·0
J. B.	68	65	6·8	0·09	2 0	8·3	7·6	5·5	4·8	4·3	1·5	1·3
A. S.	64	78	8·6	0 10	2·5	5·2	9·5	6·7	5 9	5·6	4·6	3·2
K. T.	52	87	6·0	0·10	1·9	6·2	7·3	7·0	4·9	3·8	2·4	2·1
			Mean		2·5	13·9	11·1	8·3	6·3	4·3	2·5	1·7
			± Standard deviation		1·1	8·7	4·0	3·0	2·5	1·7	1·8	1·1

Table II

Urine Concentrations of Cinoxacin (mcg/ml) after Oral Administration of 500 mg Dose

	Time (h) after administration				
Patient	0-2	>2-4	>4-6	>6-9	>9-12
W. P.	125·0	85·7	–	29·1	14·1
J. J.	106·0	111·6	110·7	67·8	10·9
I. C.	125·7	71·4	–	34·6	22·2
P. P.	164·7	410·7	60·0	54·3	37·5
C. E.	233·9	482·2	336·4	69·7	60·7
J. B.	337·2	285·7	307·2	101·8	52·9
A. S.	182·5	206·3	368·3	130·2	–
K. T.	247·6	215·9	–	147·6	131·7
Mean	192·8	233·7	236·5	79·4	47·1
±S. D.	83·9	151·2	140·8	43·3	41·8

Results

Plasma Levels. The plasma levels for each patient following the second dose of cinoxacin are shown in Table I and the mean results are shown in Figure 1. The mean peak plasma level of 13·9 mcg/ml occurred 1 hour after dosing, but in 3 patients the individual peak was reached slightly later: the peak levels showed considerable individual variation. From these plasma level data the mean half-life of cinoxacin was calculated as 4·2 ± 2·3 hours.

Urine Levels. The urinary concentration of cinoxacin is shown in Table II. The mean peak concentration occurred 4-6 hours after dosing and achieved a level approximately 20 times greater than the median MIC for most organisms commonly causing urinary tract infection (6·25-12·5 mcg/ml as measured by Black, Brier and Wolny, 1975). At 12 hours the mean urine concentration of drug was approximately 4 times the median MIC and in only 1 patient was the cinoxacin concentration below the median MIC at this time.

Tissue Levels. The prostatic tissue was obtained at times varying from 2·5-4 hours after the administration of cinoxacin and the mean tissue level was 2·3 mcg/g tissue (Table III (a)). The lowest concentration, 0·6 mcg/g, was found in a patient who had previously undergone transurethral resection and the small sample of tissue obtained on this occasion was predominantly fibrous tissue. Samples of tissue from the patient undergoing partial nephrectomy were obtained approximately 2·5 hours after administration of the cinoxacin and showed that the renal tissue concentration of the drug was 70·1 mcg/g with a concurrent plasma level of 11·7 mcg/ml. A sample of perirenal fat and of muscle taken at approximately the same time showed drug concentrations of 4·7 mcg/g and 12·6 mcg/g respectively (Table III (b)).

Side-effects

None of the patients complained of side-effects during the period of cinoxacin administration.

Discussion

In the patients we studied the plasma levels of cinoxacin showed considerable individual variation. In 4 of the patients, plasma levels during the first 3 hours after administration exceeded the mean

Table III

Concentration of Cinoxacin in Tissue (mcg/g) and Concurrent Plasma Level

(a)

Patient	Time from cinoxacin administration (hours)	Cinoxacin plasma level mcg/ml	Cinoxacin level mcg/g (prostate)
W. P.	3	9·3	6·3
J. J.	3·5	6·5	4·3
I. C.	4	7·7	1·2
P. P.	3	6·5	0·8
C. E.	3·5	4·3	1·0
J. B.	3	12·1	0·6
A. S.	3	6·0	1·2
K. T.	2·5	12·7	3·1
Mean	Mean	8·1	2·3
	S.D.	3·0	2·1

(b)

Patient	Age (yrs)	Body weight (kg)	Time from drug administration (hours)	Cinoxacin plasma level mcg/ml	Cinoxacin level mcg/g		
					Kidney	Fat	Muscle
K. M.	60	67·6	2·5	11·7	70·1	4·7	12·6

minimum inhibitory concentration for *Escherichia coli*, *Proteus mirabilis*, indole positive *Proteus* sp., *Klebsiella* sp., *Enterobacter* sp., and *Citrobacter* sp., as measured by Black, Brier and Wolny (1975). The mean urine levels of cinoxacin in the first 12 hours after administration were even greater: the mean peak levels were 20 times those of the mean MIC. These pharmacokinetic changes correspond with the high urine concentrations obtained after oral administration to rats (Holmes, Ensminger and Gordee, 1974).

The diffusion of drugs into tissues depends on the blood flow through the tissue, the concentration of drug in the plasma and the degree of binding to the blood constituents particularly plasma proteins, and the physicochemical properties of the drug such as the lipid solubility and the ionisation constant (pKa). Under the conditions of this study, blood flow through fat and muscle would be low. Thus the small concentration of cinoxacin in the perirenal fat—about one-third the concentration in muscle—could be attributed to the poor lipid solubility of cinoxacin. Cinoxacin is an acid with a pKa 4·7 and the studies in dogs by Stamey, Meares and Winningham (1970) have shown that drugs with a low pKa and poor lipid solubility do not readily diffuse into the prostate or prostatic fluid. However, other factors are also involved in the tissue uptake of drug and the high cinoxacin concentration in the kidney, one of the most vascular organs of the body, indicates that tissue blood flow and the degree of protein binding (16%) may be as important in determining tissue uptake as the physicochemical properties of the drug. In this study wide individual variations in the concentration of cinoxacin in prostatic tissue were observed: although the mean tissue level 2·5-4 hours after administration of the drug was about 25% of the concurrent mean plasma level, 2 patients achieved tissue levels approximately 66% the concurrent plasma level. There was no obvious correlation between individual tissue and plasma levels, nor any obvious relationship between tissue level and time from drug administration. The lowest tissue level was found in a patient who had previously undergone a transurethral resection of the prostate and on this occasion only a small quantity of very fibrous tissue was obtained.

In conclusion, the results from the present study have shown that after oral administration, cinoxacin is well absorbed and appears in very high concentration in the urine. Diffusion into the prostate occurred in all patients but wide individual variations were observed which seemed to be more dependent on inter-subject differences than the inherent physicochemical properties of the drug. The ultimate usefulness of cinoxacin in the treatment of prostatitis caused by susceptible organisms will only be shown by the clinical investigation of suitable patients.

Summary

Cinoxacin, a synthetic antibacterial compound, was given orally in a dose of 500 mg to 8 patients undergoing transurethral prostatectomy.

The drug was well absorbed and the peak plasma level (mean 13·9 mcg/ml) occurred 1 or 2 hours after administration. Concentrations of cinoxacin in the urine reached a peak (mean 236·5 mcg/ml) 4 to 6 hours after dosing, and remained higher than the mean MIC for most common urinary pathogens for 12 hours after administration.

The concentration of cinoxacin in prostatic tissue 2·5-4 hours after administration varied between 0·6 and 6·3 mcg/g. The individual variations were unrelated to the concurrent plasma level and appeared to be influenced more by inter-subject variation than by the physicochemical properties of the drug.

In 1 patient the cinoxacin level was estimated in renal tissue (70·1 mcg/g), in muscle (12·6 mcg/g), and in perirenal fat (4·7 mcg/g).

We wish to thank Professor John Blandy for his help with the study and for allowing us to investigate patients in his care. We are also grateful to our nursing colleagues for their help during the study.

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The Authors

R. A. P. Burt, FFARCS, Director of Clinical Investigation, Lilly Research Centre.
T. Morgan, FRCS, Senior Surgical Registrar, St. Peter's Hospital.
J. P. Payne, FFARCS, Honorary Consultant Anaesthetist, St. Peter's Hospital.
R. M. Bonner, MIBiol, Scientific Officer, Lilly Research Centre.

Requests for reprints to Dr R. A. P. Burt, Lilly Research Centre Ltd., Erl Wood Manor, Windlesham, Surrey, GU20 6PH.

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Guided Dilatation and Transurethral Resection in one Session for Treatment of Post-prostatectomy Obstructive Complications

G. MOBILIO, S. COSCIANI CUNICO and S. PETRACCO
Department of Urology, University of Padua, Padua, Italy

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Stenosis of the vesical neck and the prostatic fossa may be late complications of prostatectomy. Their incidence varies from 3 to 4% (Meinardi, 1962, Weyeneth 1968) to more than 20% (Caine) 1954 depending on which symptoms are considered indicative of the condition. Accordingly, the incidence of obstructive alterations following prostatectomy will vary markedly depending if one considers dysuria alone to be a symptom, or if dysuria is discounted as a symptom if good urethral canalisation is demonstrated by means of cysto-urethrogram. In fact, frequent micturition, burning during micturition, or persistent leukocyturia following prostatectomy may often indicate stenosis.

If normal healing does not follow surgical removal of an adenoma, the prostatic fossa may shrink and assume different morphological features depending on whether the fibrosis involves the entire area from the bladder neck to the verumontanum (prostatic urethral stenosis) or whether it is limited to only a thin diaphragm between the bladder and the prostatic fossa (bladder neck stenosis).

Employing both guided dilatation and transurethral resection (T.U.R.) in a single operating session, we have treated 53 patients with post-prostatectomy obstructive complications above the colliculus seminalis. The results have prompted us to write this report.

Patients

The types of prostatectomy which had resulted in the stenoses were:—transvesical prostatectomy, 35 (24 bladder neck stenosis and 11 prostatic urethral stenosis); retropubic prostatectomy, 18 (15 bladder neck stenosis and 3 prostatic urethral stenosis).

Methods

In order to perform T.U.R. the resectoscope must enter the bladder. Penetration of the stenotic tissue may be achieved by 1 of 2 methods.

The first, surgical diathermic penetration, is accomplished by pushing the diathermic loop of the resectoscope against the stenotic tissue, from the urethra towards the bladder, thus creating an opening which will allow the resectoscope to pass (Fig. 1).

This procedure, however, is not without risk, for if the direction of the loop is incorrect the prostatic capsule may be perforated (Fig. 2). This hazard may be avoided by employing the second technique: guided dilatation.

With the patient under epidural anaesthesia, the site of the stenotic urethral orifice, often situated in an eccentric position, is located using a urethroscope. A no. 4-5 Ch. ureteric catheter is then introduced through the urethroscope. Drops of urine through the catheter indicate entry of the bladder, and the urethroscope is removed (Fig. 3a).

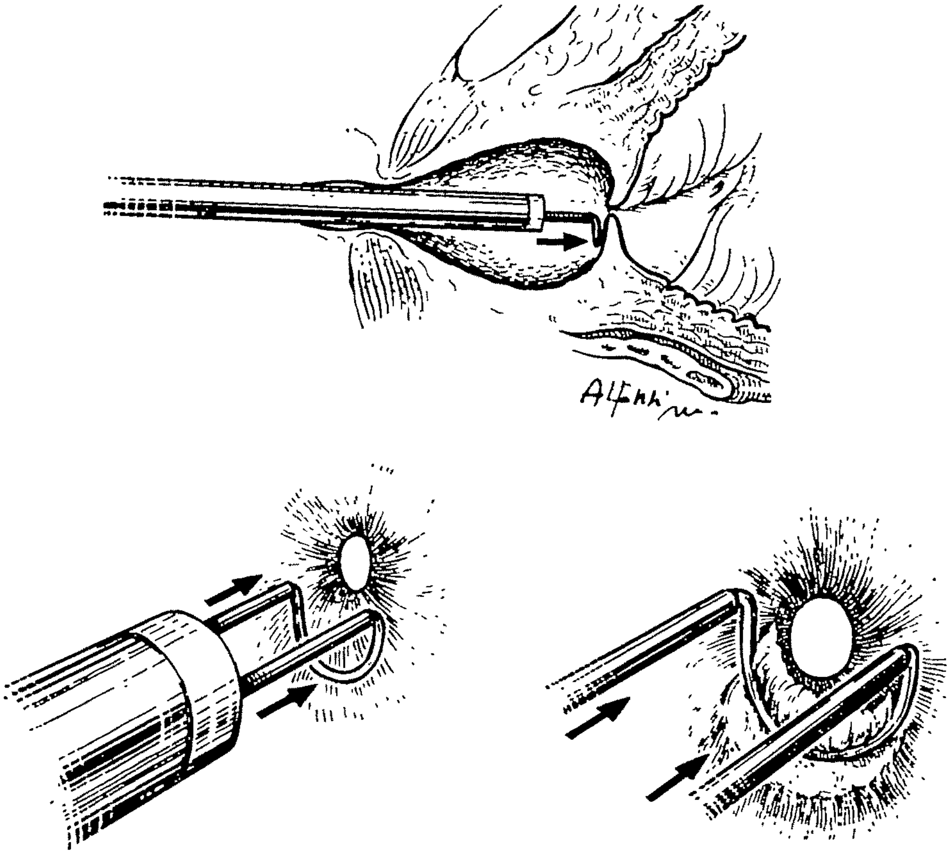


Fig. 1. Diathermic penetration of bladder neck stenosis. The diathermic loop is pushed against the stenosing tissue.

Dilatation is initiated by means of Heywalt-May straight metallic catheters which are slipped over the ureteric catheter. Easy motion of the ureteric catheter within the lumen of the metallic catheter indicates that the dilatation is proceeding correctly (Fig. 3b). If this movement is hampered, the metal catheter is not in line with the urethral orifice (Fig. 4a), and the direction of the metal catheter must be modified (Fig. 4b). The urethra is dilated progressively up to 28 Ch. gauge metal catheters and then, in the same session, the resectoscope is introduced. No difficulty will be encountered in reaching the bladder. T.U.R. of the stenosing fibrous tissue may begin immediately. It is possible to follow resection visually and there is no risk of perforation (Fig. 5). Relative to traditional procedures, guided dilatation offers more security not only because the guiding ureteric catheter is introduced through the stenotic orifice under visual control, but also because the catheter itself affords a means of controlling the progress of the dilatation.

Results

We have employed guided dilatation followed by T.U.R. in the same operating session on 53 patients. 26 cases followed prostatectomy performed at this clinic and 27 cases followed prostatectomy performed elsewhere. 39 cases presented bladder neck stenosis and 14 cases presented prostatic urethral stenosis. This treatment has been applied, in some cases even soon after the prostatectomy, when obstruction was indicated by clinical and radiological (ascending and voiding urethrogram) data.

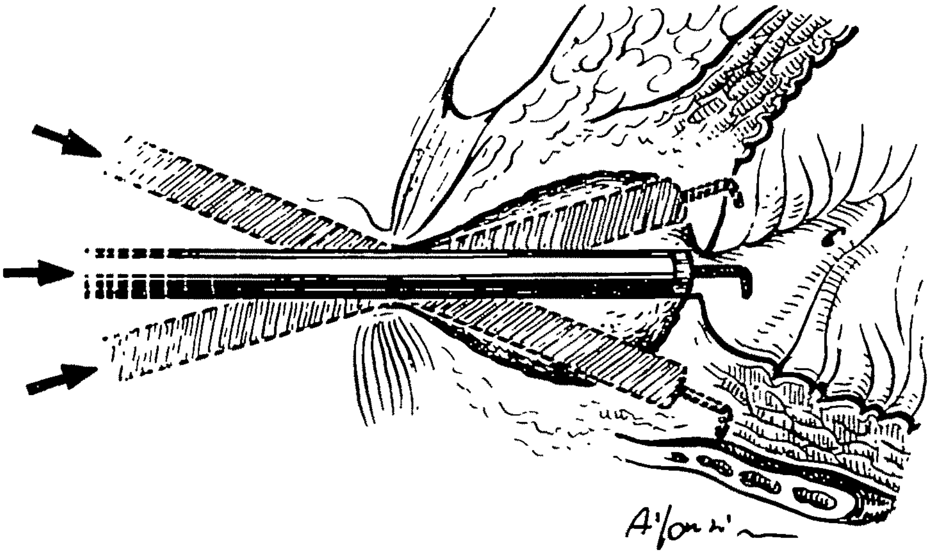
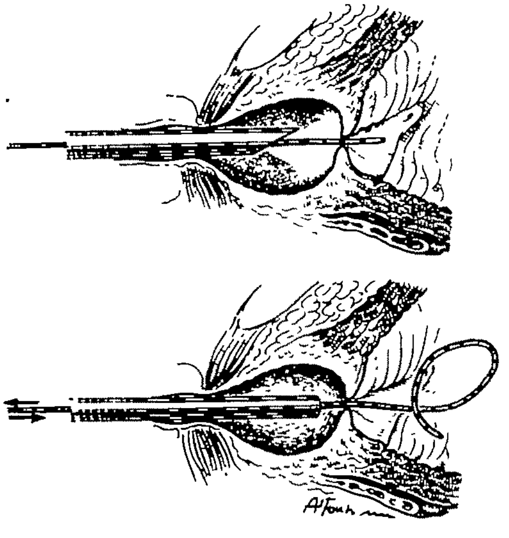


Fig. 2. The prostatic capsule may be perforated if the direction of the diathermic loop is incorrect.



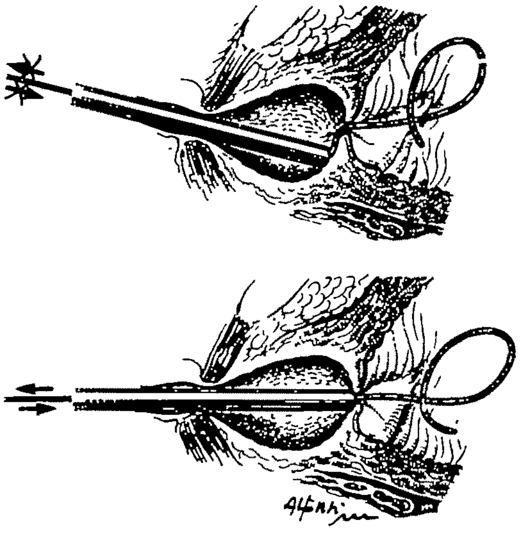


Fig. 3. (left) Introduction of the 4-5 Ch. ureteral catheter through the stenotic orifice by means of the urethroscope.

Fig. 4. (right) Guided dilatation by means of straight metallic catheters along the ureteral catheter. Top figure shows incorrect position; bottom figure shows correct position.

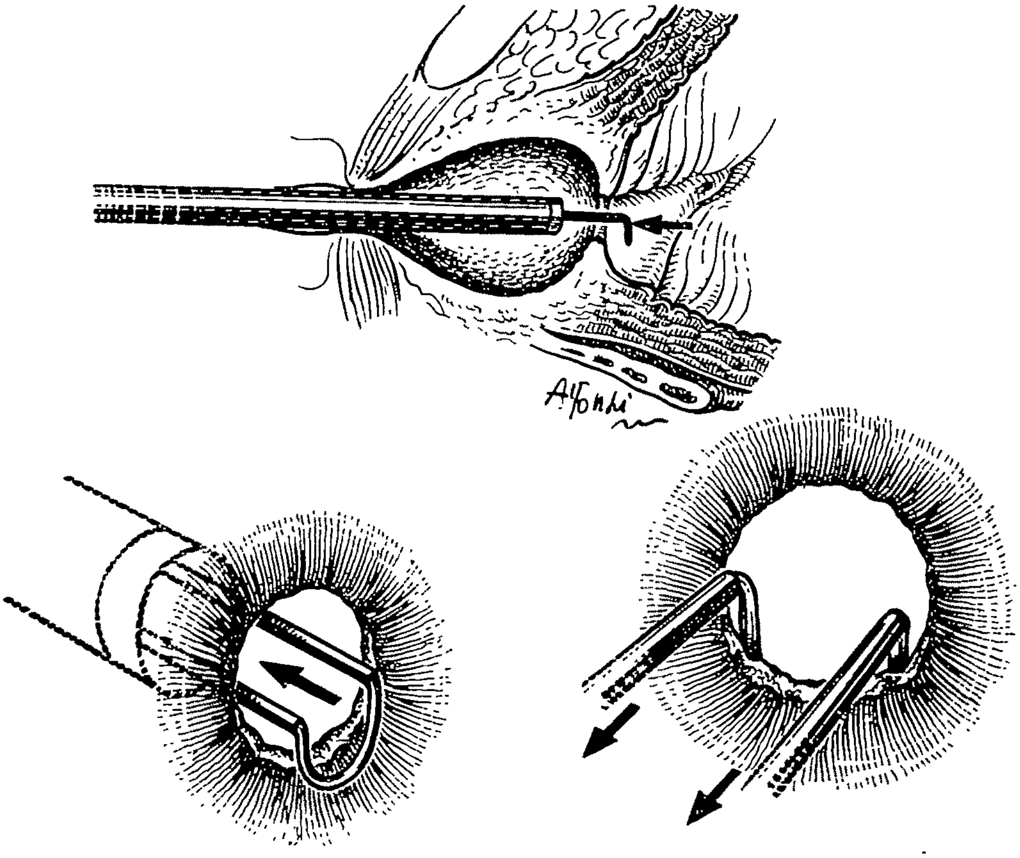


Fig. 5. T.U.R. of the stenosing fibrous tissue may begin immediately after dilatation.

Dilatation has always been sufficient for the easy introduction of the resectoscope. We have not observed false passage or perforations. Once the resectoscope is introduced, resection of the stenosing fibrous tissue is comfortably carried out since the external sphincter, the bladder neck as well as the ureteric orifices are under constant visual control.

Upon completion of T.U.R., an indwelling Foley catheter is inserted for 2-3 days. In 7 cases, however, the stenosing diaphragm was particularly thin, haemostasis was perfect, and the urine was sterile and therefore catheter drainage was not required. In 5 cases, there was associated calculosis. In 4 of these the calculi were either small or single and electrolithotrity was performed in the same session. In the fifth case, the calculi were large and, to minimise the risk of infection, we preferred to wait several days before proceeding with electrolithotrity in this patient.

Table I summarises our results which were controlled from 3 to 12 months following resection. We considered excellent those cases in which a single TUR yielded stable canalisation and rapid sterility of the urine (Fig. 6). When these same results required a second T.U.R., the cases were deemed satisfactory (Fig. 7). Unsatisfactory results were scored when stenosis recurred despite repeated T.U.R. (Fig. 8).

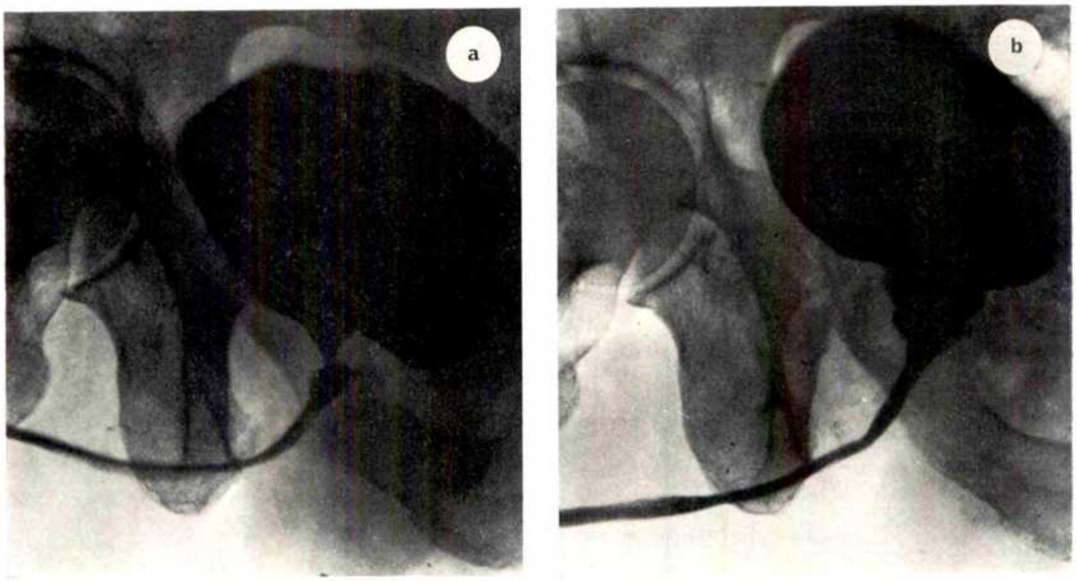


Fig. 6. bladder neck stenosis after prostatectomy. Micturating cystourethrogram before (a) and after (b) T.U.R. Excellent results.

Table I
Results of Guided Dilatation and T.U.R. in a Single Session for the Treatment of Post-prostatectomy Urethral Stenosis above the Colliculus Seminalis

Type of stenosis	(Total)	Excellent	Satisfactory	Unsatisfactory
Bladder neck stenosis	(39)	34 (87%)	5 (13%)	–
Prostatic urethral stenosis	14	1 (7%)	2 (14%)	11 (79%)

Conclusion

In all our cases of stenosis above the colliculus seminalis following prostatectomy the technique of guided dilatation had permitted the resectoscope to reach the bladder while avoiding the hazards of blind dilatation or surgical diathermic penetration (perforations, false passages, or lesions of the ureteric orifices). The results obtained with T.U.R. were very good in cases of bladder neck stenosis. Unsatisfactory results were yielded in cases of prostatic urethral stenosis because persistent canalisation of the urethra was usually not achieved even if T.U.R. was extended to all the stenosing fibrotic tissue.

After repeated resections in these cases we resorted to surgical repair of the stricture.

From our experience, it appears particularly advantageous to perform guided dilatation and T.U.R. in 1 session since the patient's stay in hospital is shorter, the risk of infection is reduced, and the resection is facilitated since the tissue is not previously injured by a permanent catheter.

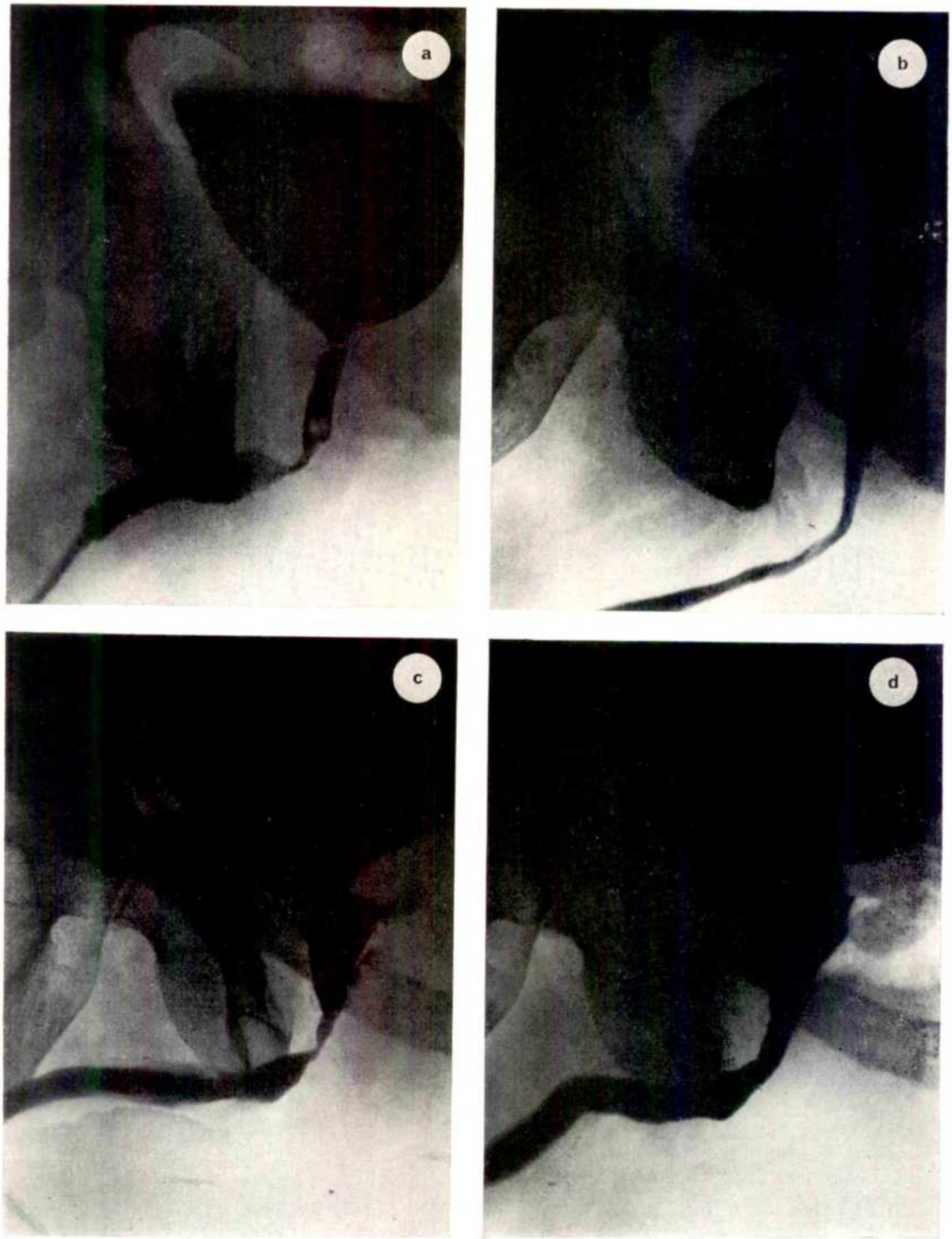


Fig. 7. Bladder neck stenosis after prostatectomy. Micturating urethrogram before (a) and 1 month after (b) T.U.R. Stenosis recurred after 3 months (c). After second resection (d). Satisfactory results.

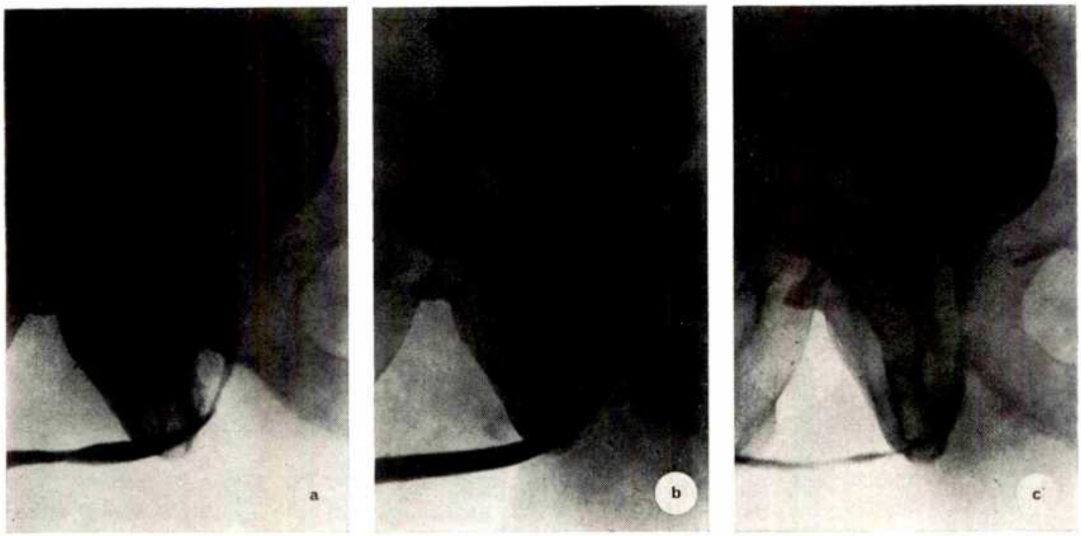


Fig. 8. Prostatic urethral stenosis after prostatectomy: micturating urethrogram. Unsatisfactory results after 3 T.U.R.s (a). In spite of the fourth T.U.R. (b) there was recurrence of the stenosis (c). Unsatisfactory results.

Summary

53 patients presenting with post-prostatectomy obstructive complications above the colliculus seminalis were treated in a single session by means of guided dilatation of the stricture followed by transurethral resection of the stenosing fibrotic tissue.

No failures or complications with the guided dilatation technique have been observed.

The results obtained after resection in cases of bladder neck stenosis were very encouraging.

Unsatisfactory results were observed in cases of prostatic urethral stenosis because resection is not a technique sufficient for stable resolution of the obstruction.

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The Authors

Gaetano Mobilio, MD, Director, Urologic Clinic.
Sergio Cosciani Cunico, MD, Professor of Surgical Nephrology.
Sergio Petracco, MD, Assistant Urologist.

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Short Case Report

Thioridazine-induced Priapism

Priapism is a persistent painful penile erection unrelated to sexual activity and affecting only the corpora cavernosa, sparing both the corpus spongiosum and glans penis. In a number of cases the aetiology has been drug induced (Rubin, 1968; Dawson-Butterworth, 1970; Osborne, 1974). A case of priapism induced by acute thioridazine (Melleril) overdose is presented with consideration to possible mechanisms of pathogenesis.

Case History

A 24-year-old white male was admitted to Yale-New Haven Hospital with a 48-hour history of persistent erection that had begun 2 hours following the ingestion of 50 capsules (25 mg) of thioridazine in a suicide attempt. It was noted that the patient had not been hypotensive or comatose when he first sought psychiatric assistance immediately following ingestion of the thioridazine. The patient reported his painful erection 2 days after the suicide attempt and examination of the genitalia revealed firm and tender corpora cavernosa with a soft glans penis and corpus spongiosum. The patient had no prior genito-urinary or haematologic disorder. Various haematologic studies were unremarkable.

Spinal anaesthesia and evacuation of the sludged blood by irrigation of the corpora did not alter the priapism. A left corpus cavernosum-to-corpus spongiosum shunt lessened but did not alleviate the priapism and a right saphenous vein to right corpus cavernosum anastomosis resulted in further reduction in the penile turgor. The use of intermittent penile compression and anticoagulation resulted in total penile detumescence within 12 hours. Several days postoperatively the patient had a physiological erection that responded to amyl nitrite with instantaneous detumescence.

Comment

Drugs reportedly associated with the development of priapism all have hypotensive effects secondary to alpha sympathetic blockade and pelvic venous thrombosis must be considered a possible aetiology. In this case venography did not demonstrate pelvic venous thrombosis.

An alternative mechanism may be that drug-induced sympathetic blockade allows parasympathetic predominance with resultant priapism by closure of the venous channels of the penis. This is supported by the report by Osborne (1974) who resolved priapism induced by a phenothiazine with intravenous benztropine (Cogentin), an acetylcholine antagonist. If erection is due to parasympathetic action with detumescence requiring sympathetic activity (Rubin, 1968), then medical treatment of priapism might be feasible. However, there are no reports of spontaneous erections due to cholinergic therapy alone.

A third possible explanation could be an extrapyramidal effect of thioridazine inducing spasm of the ischiocavernous muscles resulting in compression of the venous drainage of the corpora cavernosa.

Treatment of priapism should be rapid, perhaps with a trial of an acetylcholine antagonist before surgical venous shunting. It is encouraging that potency was restored in this patient even though surgery was performed after 2 days of priapism.

R. A. Appell, D. E. Shield, E. J. McGuire
Department of Surgery, Section of Urology, Yale University School of Medicine, New Haven, Connecticut.

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Address for reprints: Dr R. A. Appell, Lecturer in Urology, London Hospital Medical College, Whitechapel, London E1 1BB.

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Hormonal Pattern in Prostatic Carcinoma following Orchidectomy: 5-Year Follow-up

U. BRACCI, F. DI SILVERIO, F. SCIARRA, G. SORCINI, C. PIRO and F. SANTORO
Institute of Urology and Institute of Patologia Medica,
University of Rome, Rome, Italy

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In a previous report it was demonstrated that in patients with Flocks stage C prostatic adenocarcinoma showing clinical improvement following orchidectomy, plasma testosterone (T) concentrations fall to levels comparable to those of normal women (Sciarra *et al.*, 1973). In a few cases, however, not benefiting from surgery, T, 30 and 60 days after orchidectomy, was still above 100 ng/100 ml.

In the present investigation clinical and hormonal findings have been collected from patients affected by carcinoma of the prostate observed over a 5-year period following orchidectomy. Plasma T, gonadotropins (FSH-LH) and cortisol (F) were repeatedly determined and an attempt was made to establish correlations between hormonal and clinical findings.

Materials and Methods

14 patients, aged 61-78 years, affected by Flocks stage B or C prostatic carcinoma were studied before and after bilateral orchidectomy. None of these patients had received hormone therapy at any time. Tissue specimens obtained by transrectal biopsy prior to surgery revealed the presence of prostatic adenocarcinoma with moderate anaplasia (Mostofi's classification Grade 2) in 10 cases (nos. 1-10) and adenocarcinoma with slight anaplasia (Grade 1) in 4 cases (nos. 11-14).

Blood samples for the determination of T, FSH-LH and F were collected at 8.30 a.m. on the day of orchidectomy, whereas after surgery T was evaluated every 3 months and the other hormones after 1 and 5 years. Rectal exploration, urography and phosphatase determinations were carried out in all these patients every three months.

Plasma T was evaluated according to the competitive binding technique already described (Sciarra, Sorcini and Piro, 1969; Sciarra *et al.*, 1971) using 2% third trimester pregnancy plasma in 0·9% (W/v) saline solution as the source of testosterone binding globulin. Normal T values are 620 ng ± 160 SD/100 ml for adult males and 62 ng ± 22 SD/100 ml for adult females.

Plasma gonadotropins FSH and LH were determined according to the procedure of Wide (1969), slightly modified by Fraioli (1970). Normal FSH and LH values in adult men are 2·5-9 mIU/ml and 2-12 mIU/ml respectively.

Plasma cortisol was determined with the competitive protein binding technique described by Murphy (1967) using 2·5 ml of dog plasma in 100 ml distilled water as the source of CBG. Normal values of plasma cortisol at 8.30 a.m. are 6-18 μg/100 ml.

Results

Hormonal Findings

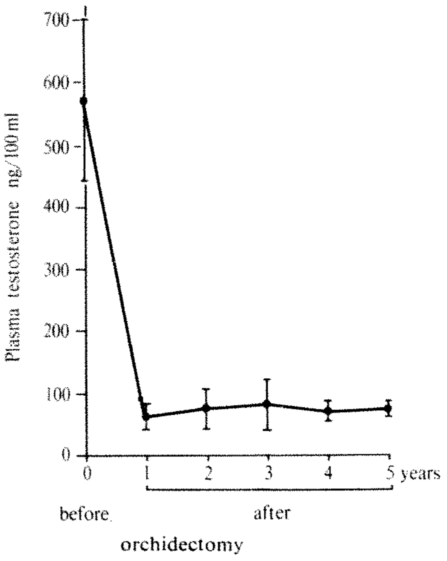
The mean values of plasma T before and after orchidectomy in the 14 patients affected by prostatic adenocarcinoma are shown in Table I and Fig. 1. It can be seen that:

1. T was within normal limits before castration (571 ng ± 138 SD/100 ml and decreased significantly after surgery (62 ng ± 21 SD/100 ml).

Table I

Plasma Testosterone Determination Before and After Orchidectomy in Cases of Prostatic Adenocarcinoma

		Tumour		Testosterone (ng/100 ml)						
					Post-orchidectomy (years)					
Patients	Age	Grade (Mostofi)	Stage (Flocks)	Basal	1	2	3	4	5	Tumour at 5 years follow-up
1. F. M.	71	2	B	430	110	144	176	110	100	Partial regression
2. G. A.	66	2	C	590	88	112	40	68	92	Regression
3. A. C.	64	2	B	620	84	86	62	84	73	Regression
4. D. C.	71	2	B	900	88	84	88	72	75	Regression
5. L. D. F.	67	2	B	720	64	42	58	64	71	Regression
6. S. P.	78	2	C	411	52	56	67	54	70	Increased
7. G. F.	76	2	B	444	60	46	54	61	66	Regression
8. Q. M.	73	2	C	710	66	51	64	71	98	Increased
9. V. A.	73	2	B	638	46	59	75	51	59	Regression
10. A. L.	71	2	B	559	72	81	92	93	83	Partial regression
11. L. F.	74	1	B	442	N.D.	34	180	64	74	Regression
12. R. D. G.	61	1	B	521	61	88	74	55	73	Regression
13. L. R.	62	1	B	530	30	76	74	75	68	Partial regression
14. U. B.	68	1	B	480	51	49	50	82	70	Regression
			Mean	571	62	72	82	71	76	
			±S.D.	138	21	30	42	16	12	



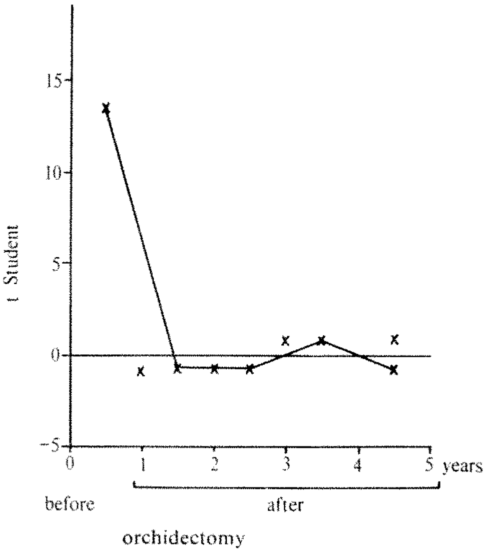


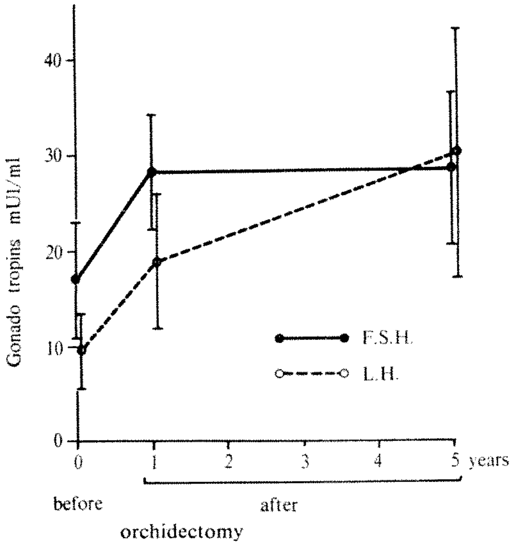
Fig. 1. Behaviour of plasma testosterone in patients with prostatic carcinoma before and after orchidectomy.

Fig. 2. Plasma testosterone before and after orchidectomy (Student *t* values).

Table II

Plasma Cortisol and Gonadotropins FSH-LH Before and After Orchidectomy in Cases of Prostatic Adenocarcinoma

	Cortisol (ng/100 ml)			FSH (mIU/ml)			LH (mIU/ml)		
		Post-orchidectomy (years)			Post-orchidectomy (years)			Post-orchidectomy (years)	
Patients	Basal	1	5	Basal	1	5	Basal	1	5
F. M.	6	16	25	23	33	35	11	31	42
G. A.	10	11	14	25	39	43	8	27	54
A. C.	9	19	17	8	32	30	13	20	31
D. C.	4	9	13	11	29	36	8	12·6	12·5
L. D. F.	7	13	15	19	27	30	6·5	19	26
S. P.	14	18	66	9	14	11	2	17·5	26
G. F.	6	9	12	13	30·5	32	12	19	25
Q. M.	14	18	59	17	24·5	N.D.	5	4·4	1·9
V. A.	9	12	12	21	32	32	12	13	26
A. L.	6	9	14	22	26	23	16	18·5	39
L. F.	10	14	14	24	31	38	10	17	26
R. D. G.	9	18	15	18	26	23	16	22·5	31
L. R.	11	13	31	22	27	35	7	14	42
U. B.	11	13	19	10	31	36	7	28·5	38
Mean	9	13·7	23·2	17·2	28·6	28·8	9·5	18·8	30·1
±S.D.	2·9	3·5	14·4	5·9	5·6	8·2	6·9	6·9	12·9



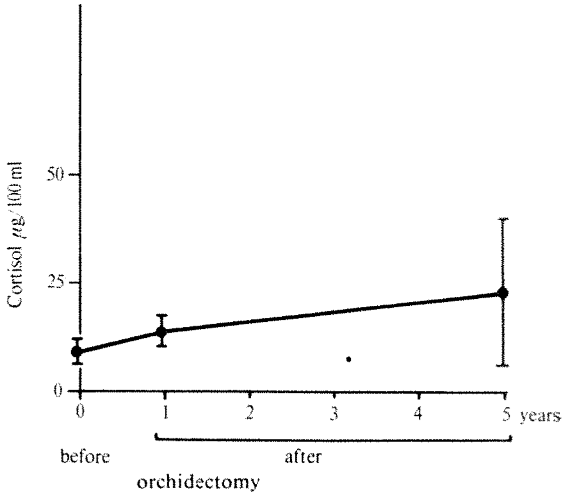


Fig. 3. Behaviour of plasma gonadotropins FSH-LH in patients with prostatic carcinoma before and after orchidectomy.

Fig. 4. Behaviour of plasma cortisol in patients with prostatic carcinoma before and after orchidectomy.

2. T values were always below 100 ng/100 ml in orchidectomised subjects, even in cases showing only partial regression or increase of the tumour.
3. Mean square deviation of testosterone values decreased progressively from the 3rd to the 5th year after orchidectomy, thus indicating that all the values are uniform and in close proximity to the mean values. The difference in values prior to and 1 year post-orchidectomy were highly significant as shown by Student *t* test ($P < 0{\cdot}0005$) after which no significant variation was found during the following years (Fig. 2).

As far as concerns the behaviour of plasma gonadotropins, it can be seen that FSH which was normal in basal conditions (17 mIU ± 5/ml) increased 1 year after orchidectomy to 28 mIU ± 5/ml, thereafter remaining constantly elevated at the 5th year post-castration (28 mIU ± 8/ml), whereas LH, which was also normal in basal conditions (9·5 mIU ± 4/ml), increased progressively up to the 5th year (18 mIU ± 6/ml and 30 mIU ± 12/ml, 1 year and 5 years post-orchidectomy, respectively (Table II and Fig. 3). A similar pattern was observed for plasma cortisol, the mean values of which increased progressively from 9/μg ± 2·9 SD/100 ml before orchidectomy to 23·2/μg ± 17·4/100 ml at the 5th year post-orchidectomy (Fig. 4). In cases 1 and 13, showing partial regression of the tumour, and in cases 6 and 8, showing an increased tumoral mass with bone metastases, plasma cortisol rose to 25, 66, 59 and 31 μg/100 ml, respectively (Table II).

Clinical Findings

At the control examination 5 years after orchidectomy, the rectal exploration demonstrated regression of the tumour almost to the intracapsular stage in 9 patients (nos. 2-4, 7, 9, 11, 12, 14), a partial regression in 3 patients (nos. 1, 10, 13), whilst in 2 patients (nos. 6 and 8) the tumoral mass showed a further increase with diffuse bone metastases (Table I).

Discussion

Orchidectomy or the administration of oestrogens and anti-androgens such as cyproterone acetate in the treatment of advanced and metastatic adenocarcinoma of the prostate is aimed at lowering testosterone production in order to inhibit the stimulus of tumour growth (Huggins and Hodges, 1941; Alder *et al.*, 1968, Di Silverio and Gagliardi, 1968; Geller *et al.*, 1968; Young and Kent, 1968).

In our experience, the best results are obtained with orchidectomy (with or without cyproterone acetate administration) which in most cases reduces plasma testosterone to values within the range of normal females and temporarily induces regression of the neoplasia (Bracci and Di Silverio, 1973).

According to other authors, however, oestrogen treatment, particularly stilboestrol, is preferable since 1 mg three times daily is sufficient to lower plasma testosterone, without inducing cardiovascular complications frequently observed with higher doses (Robinson and Thomas, 1971; Mackler *et al.*, 1972; Shearer *et al.*, 1973).

Plasma testosterone determination may therefore be an accurate monitor in the management of prostatic carcinoma. In fact, in an earlier series of investigations we demonstrated that plasma testosterone levels in patients showing a clinical remission of the tumour after orchidectomy dropped to below 100 ng/100 ml, whilst patients not benefiting from surgery showed high concentrations of testosterone (Sciarra *et al.*, 1973). Results obtained in the present investigations, however, do not confirm these findings since the testosterone values which were normal before orchidectomy fell after castration to within the range of normal females and remained below 100 ng/100 ml, 1, 2, 3, 4 and 5 years after orchidectomy in all cases, even in those showing clinical deterioration.

The reduction in plasma testosterone after orchidectomy promotes a progressive increase in plasma gonadotropins as a response of the hypophysis to the removal of the target organ.

Moreover, it is possible that ACTH is secreted in large quantities in this condition as demonstrated by Coyne and Kitay (1971) in the rat. In the present series of patients, in fact, plasma cortisol, which was normal in basal conditions, showed an increase 1 year post-orchidectomy reaching significantly elevated levels after 5 years in 4 cases who showed only a partial regression or growth of the tumoral mass with bone metastases.

High cortisol levels, therefore, may be indicative of adrenal hyperfunction which is responsible for an increased production of weak androgens that can be transformed in the prostate into more active compounds such as testosterone and DHT (Di Silverio *et al.*, 1976).

The results of Ochiai, Oshima and Srada (1969) on *in vitro* adrenal steroidogenesis in a case of prostatic carcinoma suggest that orchidectomy enhances the enzymatic activities of the adrenal cortex, resulting in increased production of corticosteroids and androgens, particularly 4-androstenedione, which in our previous investigation was found to be elevated in the plasma of some patients (Sciarra *et al.*, 1971, 1973).

These findings are in keeping with the results of Blackard *et al.* (1975) who found that 17 OHCS values of more than 20 μg/100 ml before treatment, usually indicated poor prognosis in prostatic carcinoma and death within 1 year. Fergusson and Hendry (1971), Robinson, Shearer and Fergusson (1974) and Shearer *et al.* (1973) on the other hand, demonstrated a symptomatic improvement in patients after pituitary irradiation or aminoglutethimide administration.

It is also possible that the growth of these tumours may be stimulated even by very small amounts of testosterone such as those usually found in castrated men.

In conclusion, these results suggest that after orchidectomy, cortisol and adrenal androgen determinations may be of value in detecting potential activation of prostatic adenocarcinoma.

Summary

Clinical and hormonal findings have been collected from 14 patients affected by carcinoma of the prostate observed over a 5-year period following orchidectomy.

Plasma testosterone decreased significantly after surgery (62 ng ± 21 SD/100 ml), remaining below 100 ng/100 ml even in cases showing only a partial regression or increase of the tumour. Gonadotropin FSH increased 1 year after orchidectomy to 28 mIU ± 5/ml and remained constantly elevated up to the 5th year, whilst LH increased progressively up to the 5th year (30 mIU ± 12/ml). Finally, plasma cortisol increased progressively up to 23·2 μg ± 17·4/100 ml at the 5th year post-orchidectomy, especially in those cases showing partial regression or increase of the tumoral mass, indicating an adrenal hyperfunction which is probably responsible for increased production of weak androgens that can be transformed in the prostate into more active compounds.

These results suggest therefore that after orchidectomy, cortisol and adrenal androgen determination may be of value in detecting the potential activation of prostatic adenocarcinoma.

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The Authors

U. Bracci, MD, Head, Institute of Urology.
F. Di Silverio, MD, Assistant, Institute of Urology.
F. Sciarra, MD, Assistant, Institute of Patologia Medica.
G. Sorcini, MD, Assistant, Institute of Patologia Medica.
C. Piro, MD, Assistant, Institute of Patologia Medica.
F. Santoro, Biologist, Technician, Institute of Patologia Medica.

Name and address for reprints: F. Di Silverio, Istituto di Urologia, Università di Roma, Viale del Polclinico, Rome, Italy.

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Preliminary Communication

The Use of Fine Double Siliconised Dacron in Urethral Replacement

SAID I. HAKKY

Hammersmith Hospital and the Royal Postgraduate Medical School, London

It was as early as 1880 when Duplay described his method of urethral reconstruction in hypospadias. In 1949 Denis Browne presented his modification, thus laying the foundation for Johanson (1953), Turner-Warwick (1960) and Blandy, Singh and Tresidder (1968) urethroplasties. Free skin grafts as split skin grafts (Rank, 1950), or as full-thickness skin grafts (Devine *et al.*, 1963) are also used in urethral reconstruction.

Remarkably little is known about the mechanisms that maintain or control tissue regeneration. Double-knitted siliconised Dacron mesh may act as such a stimulus—perhaps only as a scaffold—by which a new urethra may be regenerated to bridge a long deficiency. This paper reports the use of Sparks mandril (Sparks, 1973) graft, currently used in vascular surgery for urethral regeneration.

Material and Method

Nine male adult greyhound dogs 26-36 kg weight were used. All showed a normal preoperative urethrogram and with sterile urine on culture. They were divided into two groups.

Group 1. In 5 dogs 5 cm × 3 mm of siliconised double Dacron mesh round a silicone rubber rod (Fig. 1) was implanted subcutaneously in the anterior abdominal wall for 6 weeks.

At the end of this period a tube of fibrous tissue had grown around the double Dacron covering it completely (Fig. 2). Microscopically the mature fibrous tissue stained characteristically and densely eosinophilic. No epithelium was seen (Fig. 3).

This 5-cm "composite graft" of Dacron and fibrous tissue was used to replace a similar length of the mid-urethra. The silicone rubber rod was discarded and replaced by an indwelling catheter 10F for 2 weeks for urinary drainage.

Group 2. In 4 dogs, 5 cm of the double-knitted siliconised Dacron was used to replace a similar

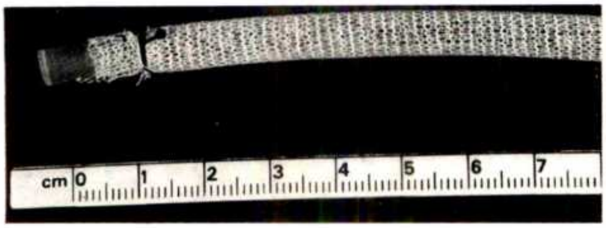

Fig. 1. Original prosthesis before subcutaneous implantation.

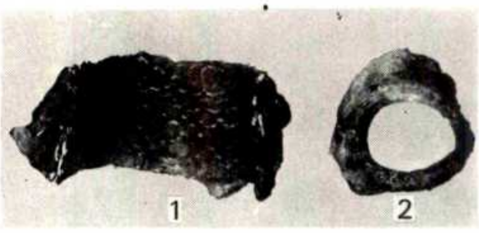

Fig. 2. Dacron mesh "composite graft" (1 and 2).

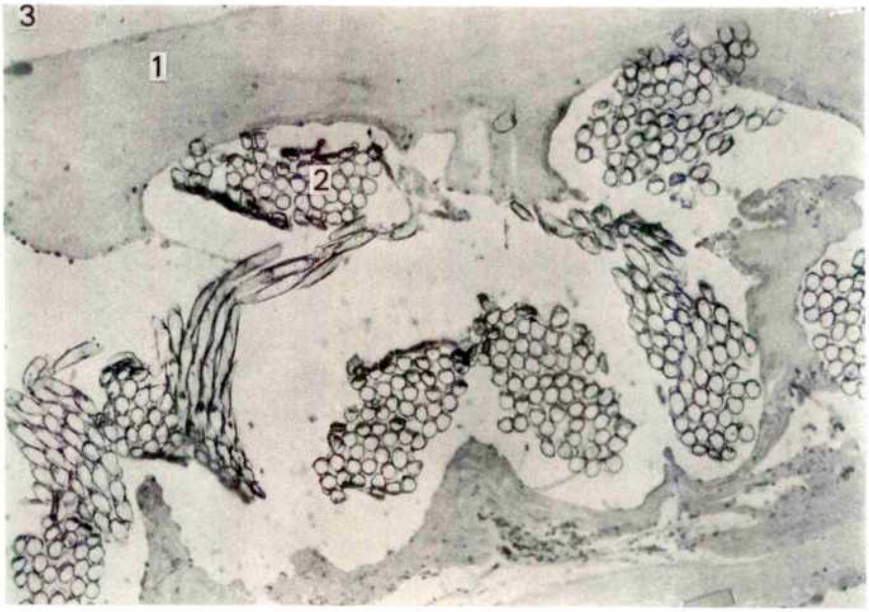

Fig. 3. Transverse section of composite graft (that is fibrous envelope and Dacron) at 6 weeks and just before urethral implantation. The inner "envelope" has few cells and is mature fibrous tissue (1), the knitted Dacron prosthesis is well seen (2) and the lumen of the implant (3) shows no epithelial lining. H and E ×400.

length of the posterior urethra at the same operation. The siliconised rubber rod was immediately discarded and replaced by an indwelling catheter 10F for 2 weeks.

At 3 months the results in both groups were assessed by ascending urethrography and, after sacrifice, by naked-eye observation and microscopy by serial sections of the urethra, stained with haematoxylin and eosin.

Results

1. *Immediate*

Only one dog (from Group 2) developed a urinary fistula through the scrotum 4 days after implantation of the graft. At post-mortem there was a distended bladder with 400 ml residual urine and the urethral catheter was found to be kinked.

In the remaining 8 dogs, the urinary stream was seen to be a dribble after removal of the catheter but returned to a normal stream within 4 weeks.

2. *At 3 months after urethral replacement* (*Group 1*)

Four dogs were sacrificed. All ascending urethrograms showed an apparent narrowing of the grafted area, but without urethral dilatation proximally or evidence of chronic urinary retention.

Macroscopic Appearance. The bladder mucosa and the urethral mucosa both proximal and distal to the graft appeared normal. In the "composite graft" area, the inner fibrous tissue appeared to have sloughed leaving the Dacron mesh exposed and only loosely attached to the new urethra, thus accounting for the apparent narrowing on the ascending urethrogram. The diameter of the new urethra, however, was similar to the rest of the urethra (3·5-4 mm). Using a magnifying glass, the lining of the grafted area was finely granular and the colour similar to the rest of the urothelium.

Microscopically. In the reconstructed area the graft was largely undermined by epithelium, but in some areas the epithelium had completely covered fragments of the graft. The epithelium was multi-layered with nuclei deeply stained. In the subepithelial layer there were abundant monocytes, lymphocytes, foreign-body giant cells and fibroblasts (both young and mature) staining deeply with haematoxylin (Fig. 4).

Two dogs in Group 2 were sacrificed after their ascending urethrograms had showed similar appearance to those in Group 1, as were the naked-eye inspections of the bladder and urethra. Microscopically, changes were similar to those seen in Group 1.

3. *At 7 months after urethral replacement*

One dog was sacrificed from Group 2, the ascending urethrogram having the apparent narrowing previously seen in both Groups 1 and 2. The naked-eye appearance of the bladder was normal and there was no residual urine. The urethral diameter proximal to the graft, at the site of reconstruction and distally was 3·5-4 mm diameter. Again in the grafted area the Dacron graft was lying almost free in the urethral lumen (Fig. 5).

Microscopically, the bladder, the urethra proximal and distal to the grafted area was normal. In the grafted area many striking features were seen (Fig. 6).

1. The lining epithelium was similar to that of the rest of the urethra and differentiation was difficult.
2. Cellular infiltration was minimal; only monocytes and lymphocytes were found in the subepithelial layer.
3. The fibroblasts had regained their usual eosinophilic staining characteristics.

Discussion

The urethra is capable of reforming its component parts over a defective area if a narrow strip

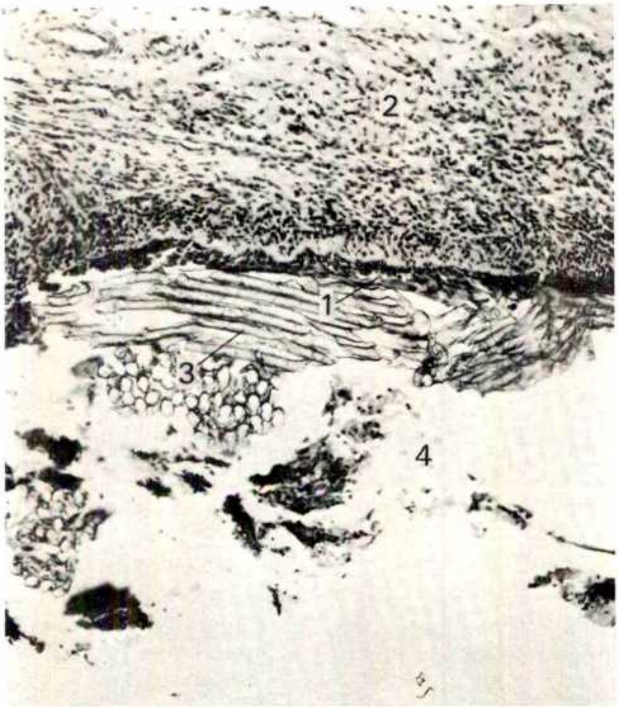

Fig. 4. Three months after implantation in urethra the "composite graft" has changed. The Dacron (3) is lying in the urethral lumen (4), but deep to this is transitional epithelium (1) with cellular fibrous tissue (2) beneath it. H and E × 150.

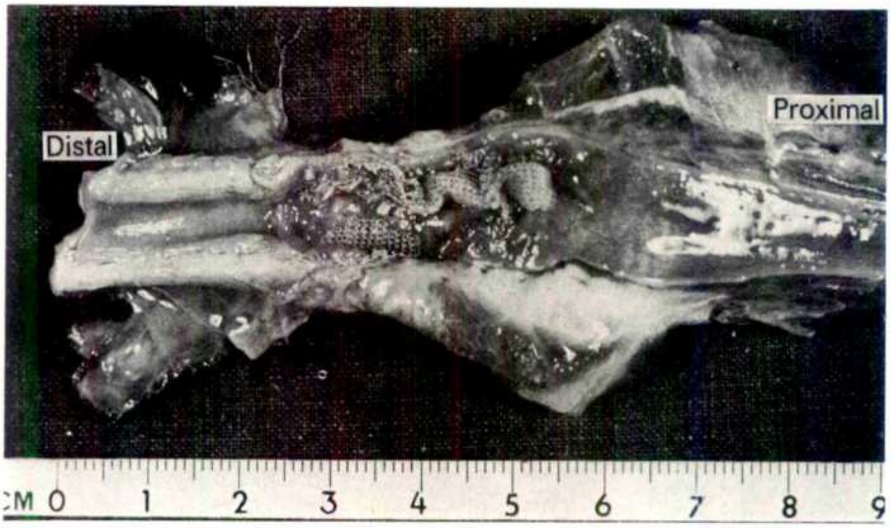

Fig. 5. At 7 months, naked-eye examination of the whole urethra shows how the Dacron graft has been extruded into the lumen (× 1·5).

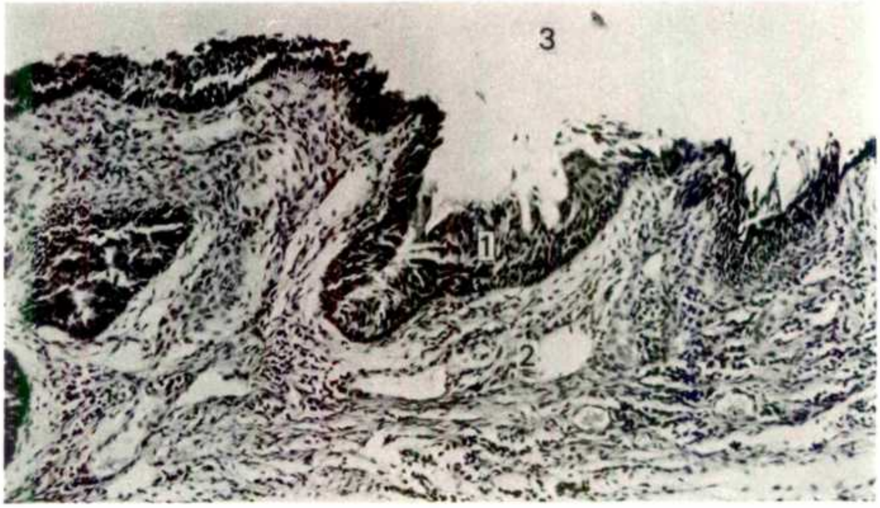

Fig. 6. Same as Figure 5, the microscopic appearances show normal-looking transitional epithelium (1), and fibrous tissue with nuclei (2), deeply lining the urethral lumen (3). H and E × 150.

containing normal urethral element bridges the gap. However, a circumferential defect of more than 1 cm in length heals by fibrous tissue, with obliteration of the lumen (Weaver and Schulte, 1962).

In the present study a special Dacron graft has been used to stimulate the host to regenerate a connective tissue tube lined by urothelium. This urothelial tube has shown no change in diameter after 7 months' observation.

The mechanism which led to the extrusion of the Dacron graft is not clear. Perhaps the epithelial behaviour in undermining the graft may in a way be similar to the behaviour of the epithelium in Ordman and Gillman's experiments (1966) on wound healing. The epithelium at the wound edge was seen to invade the suture tract deep into the dermis, thus forming a cuff of epithelium around the suture. This epithelial cuff tends to meet with the opposite side thus forming a cutano-cutaneous fistula.

Further study is now in progress both experimentally and clinically to determine the origin of the lining epithelium, to assess the role of fibroblasts and cellular infiltration and to see whether a similar stimulus is successful in the human urethra.

Summary

A knitted Dacron mesh was used to form a tube of tissue which was used to bridge at least 5-cm defect in the urethra of 9 dogs. The tube developed a urothelial lining and this showed no change in calibre after 7 months.

I wish to acknowledge the help of Professor J. P. Blandy, Professor J. C. Calnan and Mr Peter Riddle. The Iraqi Revolutionary Command Council, Minister of Health, Mr Khalid Al-Kubaisi, Mr Khairala Al-Hadithi and Mr Munaf Al-Tikriti for financial assistance. The grafts were supplied by the American Hospital Supply (UK).

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The Author

Said I. Hakky, FRCSE, Honorary Senior Surgical Registrar and Tutor.

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Short Case Report

Vesico-uterine Fistula

A 36-year-old woman presented at the out-patient clinic, with profuse and not painful haematuria coincident with the menstrual period, and slight but permanent incontinence not related with stress, 30 days after a caesarean section. The patient had had another caesarean section 2 years before with an uneventful recovery. Clinical examination, laboratory findings as well as IVP were normal.

Cystoscopy revealed the existence of a median retrotrigonal irregular depression, and the hysterographic examination confirmed a vesico-uterine communication (Fig. 1). Treatment consisted in transperitoneal transvesical closure of the fistula; the patient had a normal recovery and cure was obtained within 2 weeks (Fig. 2).

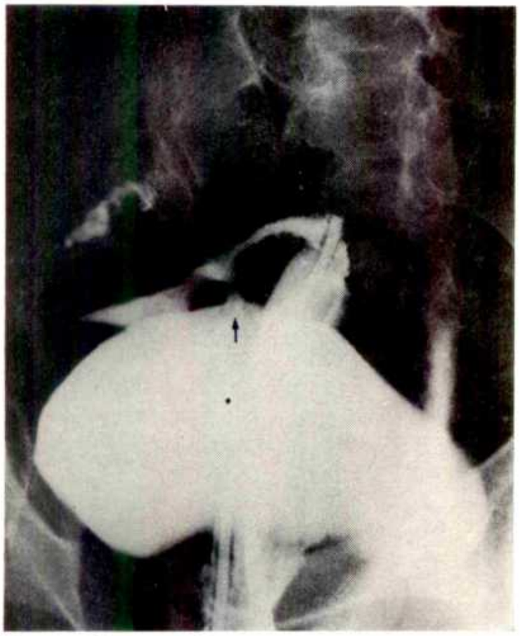

Fig. 1. Hysterography revealing the vesico-uterine communication.

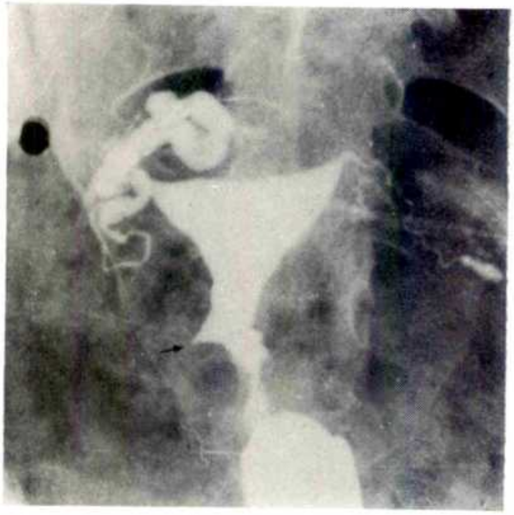

Fig. 2. Hysterography 2 months after the operation evidences the site of the previous communication.

Comment

Vesico-uterine fistula remains a very infrequent situation and almost all the cases are the result of a surgical obstetrical procedure. The main symptoms are urinary incontinence, cyclical haematuria and apparent amenorrhoea; when these last two co-exist with urinary continence we have the so-called "Youssef syndrome" (Youssef, 1960). This one-way fistula has a mechanism not yet fully understood, but it probably is concerned with an hypertonic istmic sphincter or an irregular fistulous tract.

H. A. De Carvalho
Department of Urology, Hospital Sta. Maria, Lisboa, Portugal

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The Urethral Syndrome: Experience with the Richardson Urethroplasty

A. J. SPLATT and D. WEEDON
Royal Brisbane Hospital, Brisbane, Australia

(Received 3 August 1976, accepted for publication 14 December 1976)

The problem of recurrent dysuria in females, which has been attributed to the so-called urethral syndrome, is a major one. Even though complete retention of urine in females is uncommon, it is likely that less marked bladder outflow obstruction occurs frequently. Although our experience with urethral dilatation and urethrotomy was that most of our patients gained only temporary relief from symptoms, we felt that it did give testimony to the existence of bladder outlet obstruction in females.

According to Woodburne (1961) normal micturition is the result of synchronous contraction of the detrusor with shortening and widening of the urethra. Gleason and his colleagues (1973) observed that the mechanism of obstructed voiding in females appears to be a mismatch between urethral compliance and bladder power. It is possible that the cause of this non-compliance is fibro-elastosis of the distal half of the urethro-vaginal septum as suggested by Richardson (1969). Although Richardson apparently considered that the presence of increased amounts of elastic tissue was the fundamental abnormality, Evans (1971) has regarded increasing collagenisation of the peri-urethral tissue as the cause of this outflow obstruction.

The aim of treatment in the urethral syndrome should therefore be directed to changing the non-compliant distal half of the urethra into a passive conduit. This can be done by the technique of urethroplasty described by Richardson (1969). Essentially, the technique involves excision of the band of tissue which lies between the vagina and the urethral mucous membrane in its distal half by reflecting the vagina over that area of the urethra and then reconstituting the vaginal layer.

In this paper, we report our experience with 40 patients with the urethral syndrome treated by a Richardson urethroplasty.

Patients and Methods

The age of the patients ranged from 7 to 81 years; most were in the 40 to 50 age group.

The 40 patients were personally seen by one of us (A.J.S.) initially, and also for a period of 9 to 18 months postoperatively. The possibility that these patients had bladder outlet obstruction was based, in the first place, on one or more of the following symptoms: frequency, hesitancy, an interrupted stream, and a need to strain to urinate. Detrusor hypotonia was looked for in patients who had a residual urine of more than 100 ml by means of cystometrography. 3 cases, who had a residual urine of more than 350 ml, were found to have some degree of hypotonia, but these were not excluded from the group.

36 patients were referred because they were thought to have recurring cystitis. 1 patient was referred because of stress incontinence, which was, in fact, due to a large residual urine of 500 ml. 3 patients had retention of urine. A complaint of renal-like pain was common.

The degree of urethral non-compliance was ascertained by the flow rate, the amount of residual urine, and the degree of trabeculation. Urethral calibration was used initially, but was abandoned because it did not correlate with the flow rate and the degree of trabeculation. All the cases had a urine examination, but in only 8 cases was there evidence of infection.

The average flow rate in each patient was measured by instructing her to measure the amount of urine passed at a time and record the number of seconds taken to do this. They were asked to do this on 15 consecutive occasions in the familiar environment of their own homes. If the record showed extreme variation, the test was repeated in hospital in the presence of a reliable nurse or one of us (A. J. S.). This was required on 3 occasions. A flow rate which was persistently below 20 ml per sec was regarded as being abnormal.

The amount of residual was measured by catheterisation. In those patients who had an IV urogram in which there was no residual urine in the post-micturition cystogram, this was not done.

The degree of trabeculation was noted at cystoscopy.

All of the 40 patients underwent a Richardson urethroplasty as previously described (Richardson, 1969). General anaesthesia was used. Tissue removed from the urethro-vaginal septum was examined histologically using both haematoxylin and eosin as well as Verhoeff Van Gieson elastic and connective tissue stain.

Results

Of the 40 cases, 38 showed histological changes of fibro-elastosis in the resected urethro-vaginal septum. There was a variable increase in fibrous tissue with clumping of elastic fibres. A detailed histological study of this material and control material removed at autopsy is the basis of a further study at present under way.

All 38 cases showing fibro-elastosis were relieved of their symptoms and had an increase in their urine flow rate after operation. The mean average flow rate preoperatively for the whole group was 4·9 ml per sec, while the mean average flow rate postoperatively for the whole group improved to 24·6 ml per sec.

In the 3 patients whose initial flow rate was less than 1 ml per sec prior to surgery, improvement was quite slow. 1 patient took 3 months to establish a flow rate of 20 ml per sec; another, 6 months to reach 15 ml per sec; and the third, who had retention of urine with overflow, has a flow rate of only 5 ml per sec after 9 months. Even so, this last maintains that she can urinate with a stream, whereas before treatment she had to push and strain to force an interrupted dribble. Cystometrography preoperatively revealed hypotonia which was interpreted as being due to detrusor decompensation.

Of the 38 patients who showed postoperative improvement in symptoms and urine flow rates, 2 have had a recurrence of symptoms necessitating further operation approximately 6 months after the initial operation. Both patients have had improvement in their symptoms and urine flow rates since the repeat operation, but they have been followed for only 7 months.

Two patients had histologically normal urethro-vaginal septa, and neither had any improvement in symptoms after surgery. One has subsequently admitted to taking large doses of a tranquilliser with an anticholinergic effect, and she began to pass urine normally 5 days after the drug was ceased. The cause for the other patient's retention and symptoms has not been discovered.

There were no significant complications of the procedure; in particular, incontinence was not encountered in any of the patients.

Discussion

The concept that fibro-elastosis of the urethra could cause bladder outflow obstruction in the male was put forward by Bodian in 1957. He examined histologically the urethras of 5 fatal male cases of congenital Marion's disease with comparable controls, and found that in the cases of Marion's disease there was a decrease in the musculo-glandular and an increase in the fibro-elastic elements. These were essentially the findings of Richardson (1969) in his large series of female patients in whom he diagnosed bladder outflow obstruction, and on whom he performed excision of the urethro-vaginal septum. Our studies in 38 cases have confirmed these findings. We are now attempting to ascertain the relative importance of changes in the smooth muscle, collagen and elastic tissue components of the urethro-vaginal septum by histological examination of the tissue of the area removed at autopsy and electron microscopy of tissue removed at operation. There is no agreement in the literature (Richardson, 1969; Evans, 1971) on the importance of changes in each of these components.

We considered that the flow rate method which we used would only provide an indicator of bladder emptying ability. Even though it was recognised that it would not be an accurate assessment, it was felt that it would allow of a cheap means of screening patients. We have endeavoured to show that this type of flow rate estimation, when taken together with the other parameters, provides sufficient evidence to advise definitive surgical correction, and at the same time allow evaluation of such treatment.

The presence of bladder trabeculation was regarded as another indicator of bladder outlet obstruction as it is in most cases of the same problem in males. We regard it as the visual manifestation of compensatory hypertrophy, which occurs when detrusor contraction is overtaxed whether this be the result of mechanical obstruction or unco-ordinated detrusor urethral contraction.

A clinical feature of the urethral syndrome was the frequency of the associated complaint of renal-like pain for which pyelographic studies did not reveal a cause. We think that this could be due to vesico-urethral muscle spasm as the result of unco-ordinated detrusor contraction, and that this spasm causes pain which is mediated through the sympathetic nerves to the T11 to L2 segments of the cord and referred to their dermatomes.

A criticism of the Richardson urethroplasty has been that the excised area will be replaced by fibrous scar tissue either directly or by the subsequent organisation of a haematoma in the area. It would appear that, if there is no breach in the continuity of the epithelial surfaces and that if the distance between the excised edges is great enough, a fibroblast bridge will not form and scarring will not occur. An increase in the amount of fibrous tissue was seen in the 2 cases who had to have the operation repeated. This was thought to be due to inadequate excision at the first operation.

As a result of our experience, it appears that the Richardson urethroplasty has a definite place in the management of patients with the urethral syndrome. We think that the condition of fibro-elastosis is an aetiological factor in the cause of cystitis in females, but that it can also give rise to the symptoms of cystitis in the absence of infection (only 8 out of 38 cases in this series had evidence of infection). We emphasise that the diagnosis can be made on the history, the flow rate and the presence of trabeculation.

Summary

The technique of urethroplasty described by Richardson has been used to treat 40 patients with the urethral syndrome.

38 patients have had improvement in clinical symptoms and urine flow rate following this procedure.

2 patients have had a relapse of symptoms but both have been improved by further surgery.

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The Authors

A. J. Splatt, MS, FRACS, Reader in Urology, University of Queensland.
D. Weedon, FRCPA, Anatomical Pathologist, Department of Pathology, Royal Brisbane Hospital.

Requests for reprints to: Dr A. J. Splatt, Department of Surgery, University of Queensland, Clinical Sciences Building, Royal Brisbane Hospital, Brisbane, 4029, Queensland, Australia.

British Journal of Urology (1977), **49**, 177 ©

New Equipment

Voiding Cystography in Females: a New Commode for Urine Collection*

Voiding cystography is now established as a valuable diagnostic tool, in particular when combined with bladder pressure/flow studies. To study the function of the bladder base and urethra, it is essential to view the patient in the oblique and lateral positions (Hutch, 1972).

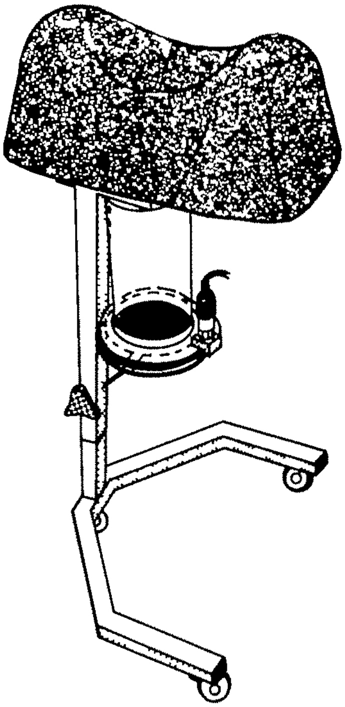
The current technique is to ask the patients to micturate in an upright position into a urinal (Raghaviah, 1976); this is frequently the cause of much embarrassment to them as they often wet themselves and the floor. Equally important is the fact that positioning the patient to void urine in an unnatural posture imposes psychological stress, which is liable to alter the pattern of voiding. It was, therefore, essential to try to find a simplified, near-natural method of voiding in the seated position during this examination.

The "Saddle Commode" design, which has been in use at this unit, has the advantage of being simple, inexpensive, easy to handle with adjustable height and rotatory movements; it is suitable for use with almost every make of conventional X-ray table. It is comfortable for the patient to sit on during voiding.

A good quality X-ray exposure of the bladder base and urethra are obtained in the oblique and lateral positions without the interposition of the thigh bones, thus minimising the dosage of radiation needed. Urine is collected directly into a measuring jug or a flowmeter, as required.

The author would like to thank Mr C. P. Bates, Consultant Urological Surgeon, for his encouragement and guidance, and Mr R. Plant, Chief Technician, Department of Medical Physics, who made the commode.

N. I. Halawa
Urodynamic Unit, Urology Department, University of Nottingham



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Requests for Reprints to present address: N. I. Halawa, DGUS, FRCS, 3 Pasteur Street, Alexandria, Egypt.

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* The design of the commode is patented under No. 36228.

British Journal of Urology (1977), 49, 178 ©

Book Reviews

A Renal Failure Diet Manual Utilizing the Food Exchange System. By M. E. Spitzer *and others.* Pp. 121. Springfield, Ill.: Thomas, 1976. $7.50.

This book is designed to be read and used by patients with renal failure and consists of a short text providing an outline of the principles of diet in renal failure followed by recommended diets.

The major criticism of the book is that some of the foods referred to may not be known outside the United States. In addition a glossary of both medical and food terms (*e.g.* cookie = biscuit) would be useful.

Despite these shortcomings the book fulfills a need and will be found useful by renal patients.

R. W.

Urological Radiology of the Adult Male Lower Urinary Tract. By R. W. McCallum and V. Colapinto. 1st Edition. Pp. vii+358 with 250 illustrations. Springfield, Ill.: Thomas, 1976. $35.50.

Since the first discovery of the possibility of demonstrating the urinary tract by X-rays, the practise of urology has been closely associated with radiology. Despite the close links between the two specialties it is unusual to find a textbook produced as a collaboration between a urologist and a radiologist. This book is the result of such a collaboration and it is clearly well worth while.

It is a pity that the authors have limited themselves to the male lower urinary tract. Despite the obvious differences, the two sexes have a lot in common and a comprehensive book would have been more useful. This is the only major criticism of a book which will be of interest to both urologists and radiologists.

It gives a very good account of the radiological techniques and findings, putting them in the context of the surgical problems. The references are excellent and surprisingly up-to-date. Unusual techniques, such as triple-contrast cystography and fractionated cystography, are described but also critically evaluated in relation to the clinical problem, for example, in staging of carcinoma.

One surprising omission is the lack of any account of urodynamic procedures. These are being increasingly used and both urologists and radiologists are looking for guidance about the usefulness of these techniques. There is also very little about the radiological investigation of intersex problems.

The illustrations are generally of high quality with only a few failing to show clearly the features they are intended to show. Like many books with radiographs the illustrations are often well separated from the text which can make reading difficult. Publishers should make more effort to overcome this problem.

W. S.

Announcements

Stiftung C.-E. Alken Prize for 1977

An endowment fund under the name of Stiftung C.-E. Alken for the furthering of clinical work and research in the field of Urology has been established to provide an annual award of SwF. 10.000 for outstanding scientific endeavours.

Regulations
The award will be for an unpublished work in the field of Urology. It will be conferred prior to the annual Congress of the German Society for Urology, and an award certificate will also be presented. The prize money may be divided among several contributors.

The papers may be written in either German or English, and three copies have to be submitted by 1st August 1977 to

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Each submission must be affixed with a code word and must not bear the author's name. But, in addition, a sealed envelope labelled with the code word is to be included, containing on a separate sheet of paper the author's name and professional standing, together with the code word.

Upon receipt of the submitted paper, the Endowment Fund acquires the option to publish it. This option is entirely independent of the actual award of the prize money. The judges will be required to announce their decision to take up this option within a period of four months after the submission deadline. If by this date no such announcement has been made, the publication rights will automatically revert to the author, and his paper will be returned to him.

The adjudicators for the award will be the Board of Directors of the Endowment Fund, and their decision will be final.

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F. Eisenberger, Ch. Chaussi and K. Wanner: "Extracorporale Anwendung von hochenergetischen Stosswellen—Ein neuer Aspekt in der Behandlung des Harnsteinleidens".

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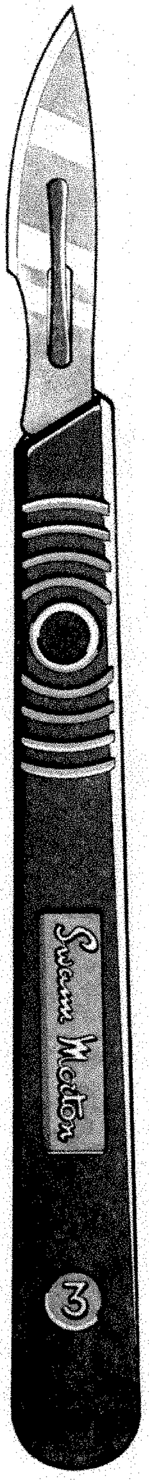

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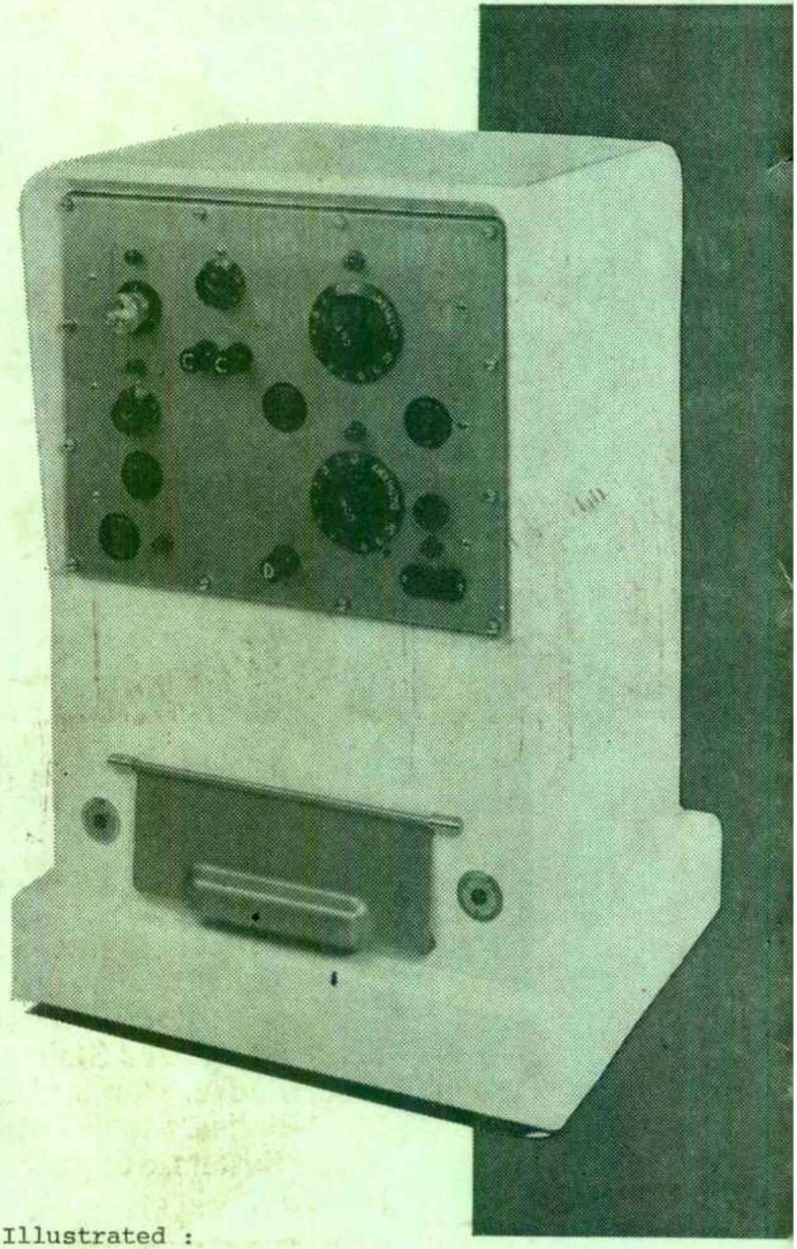

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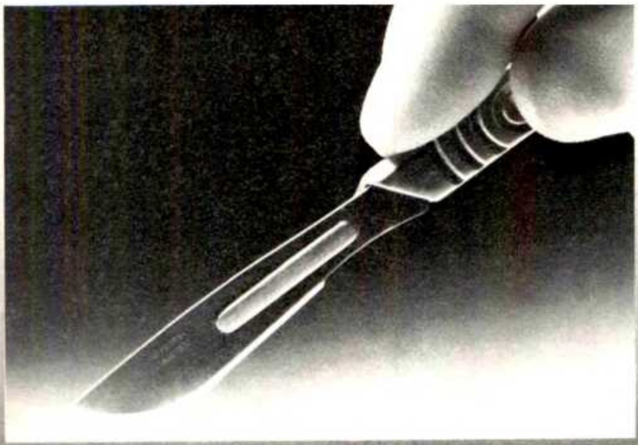

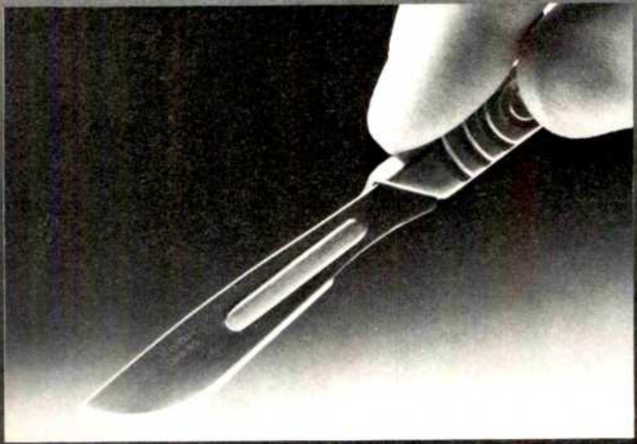

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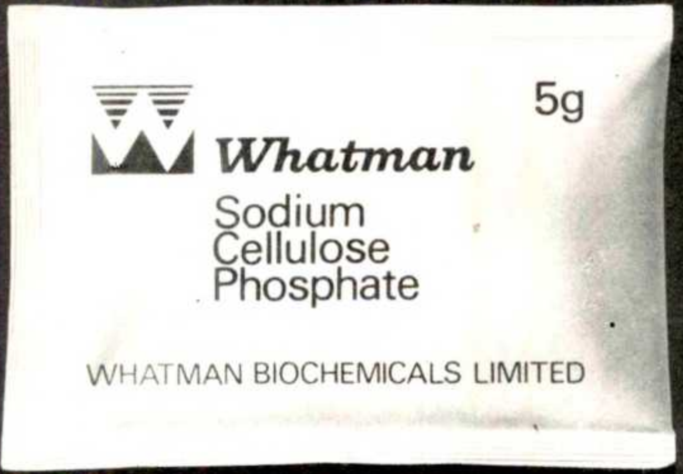

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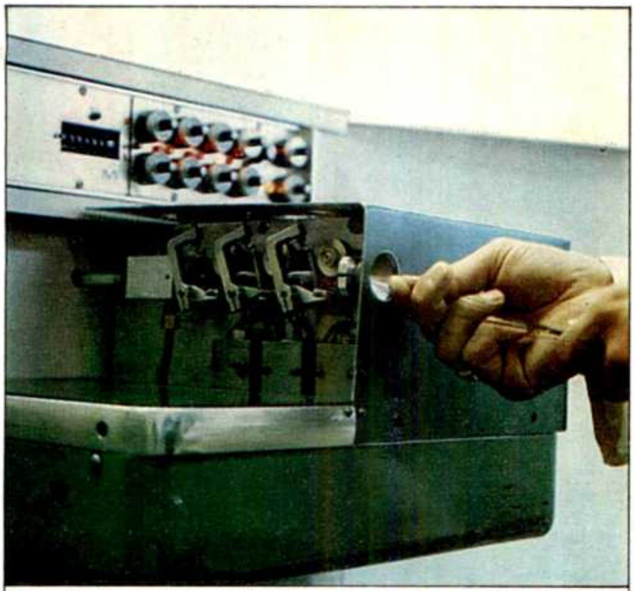
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8. Tally, F.P., *et al., Antimicrobial Agents & Chemotherapy,* **7,** 672, 1975

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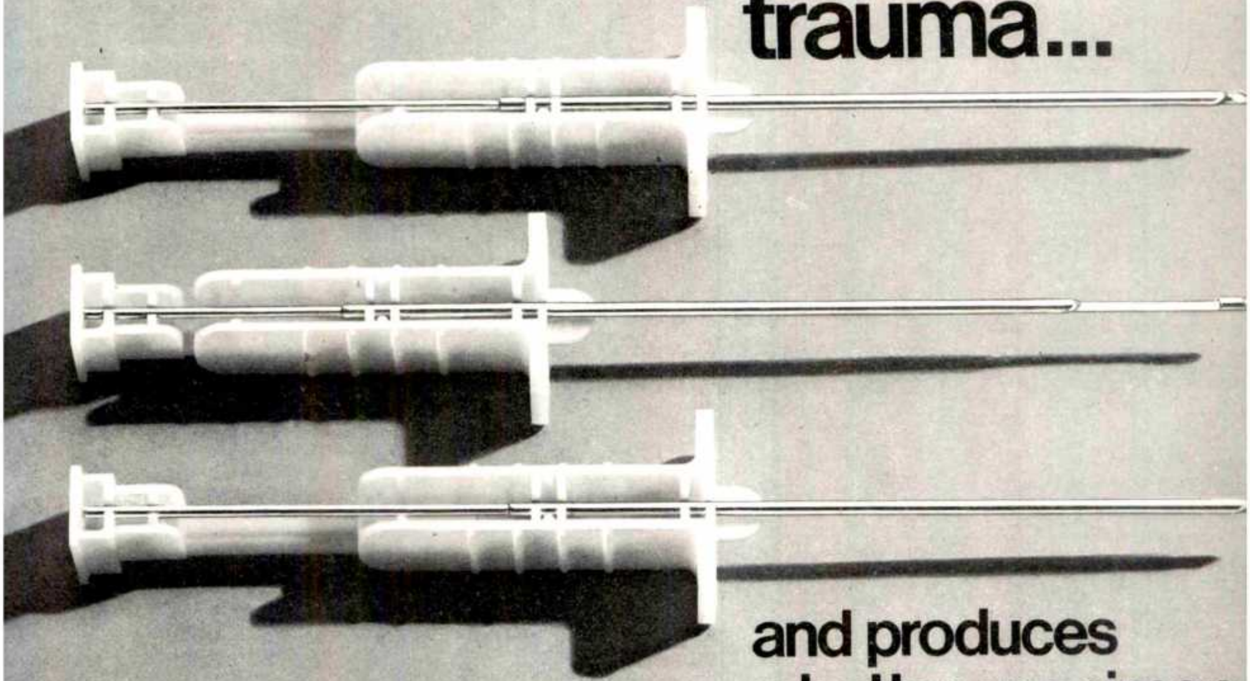

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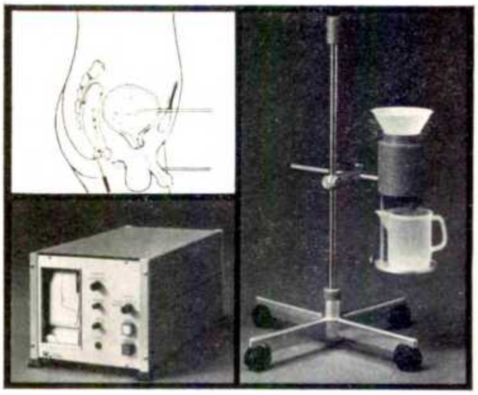

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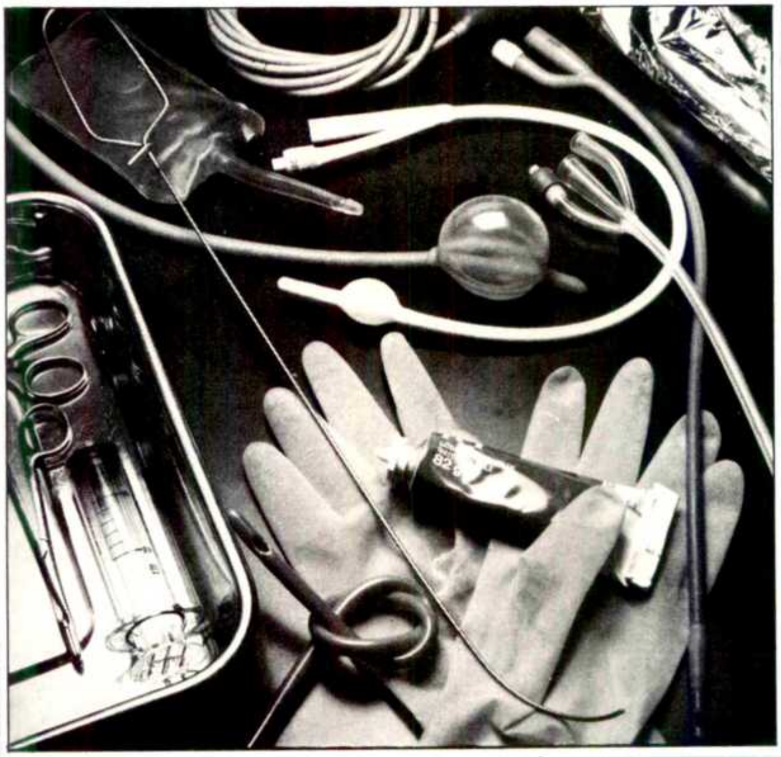

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Angiotensin Blockade in Renovascular Hypertension: A Controlled, Prospective Study

LEONARD S. MARKS, MORTON H. MAXWELL, CHERYL GROSS, UZI WAKS, and JOSEPH J. KAUFMAN

Departments of Surgery/Urology and Medicine and the Clinical Research Center, UCLA School of Medicine, and the Hypertension/Nephrology Service, Cedars-Sinai Medical Center, Los Angeles, California, U.S.A.

(Received 6 October 1976; accepted for publication 3 November 1976)

Since the Goldblatt experiments, the role of renal pressor mechanisms in renovascular hypertension has been intensively studied and debated but it has not yet been completely elucidated. A *Lancet* editor stated in 1970 that "A specific *in vivo* blocker of the renin-angiotensin system would be an extremely useful agent . . ." (unsigned editorial, *Lancet*, 1970). Theoretically, blood pressure response to angiotensin blockade would differentiate hypertensive disorders mediated by the renin-angiotensin system from other hypertensive states where the renin-angiotensin system does not play a major role in causation of the elevated pressures.

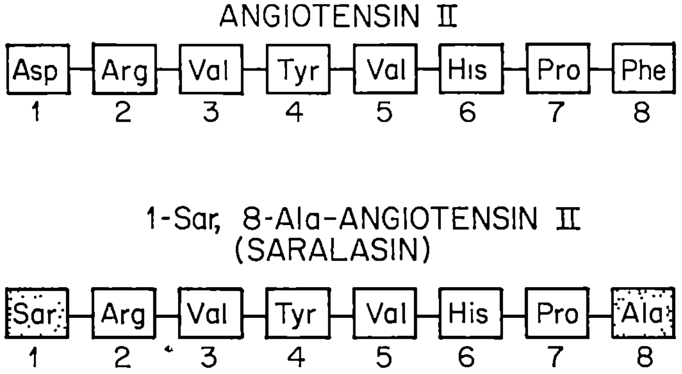

Fig. 1. Angiotensin II and saralasin. Note substitution of sarcosine for aspartic acid at the N-terminus (1-position) and alanine for phenylalanine at the C-terminus (8-position) of the molecule.

Shortly after the above editorial call appeared, such an agent, an analogue of angiotensin II (saralasin, 1-sar-8-ala-angiotensin II[1]) became available for clinical trial. Saralasin is a highly specific competitive inhibitor of angiotensin II (Fig. 1) (Pals *et al.*, 1971). In the initial human studies, a lowering of blood pressure by saralasin infusion was noted in some patients with renovascular and malignant hypertension (Brunner *et al.*, 1973; Streeten *et al.*, 1975), but not in patients with benign essential hypertension (Streeten *et al.*, 1975; MacGregor, Markandu and Dawes, 1975).

This paper was awarded a prize in the 1976 Grayson Carroll Essay Contest of the American Urological Association and was read at the annual meeting of the American Urological Association, Las Vegas, Nevada, May 1976.

[1] Eaton Laboratories, Norwich, New York.

Table I

Clinical and Laboratory Characteristics of Saralasin Responders (13 Patients) and Nonresponders (8 Patients)

				Peripheral plasma†	Renal vein renin ratio		
Patient, age, sex	Blood pressure*	Optic fundi	Serum creat.	Renin activity	Ipsilateral/ contralateral	Contralateral/ IVC	Diagnosis (lesion)‡
Responders							
M. W., 36, F	170/110	0	0·8	4858	Not done	Not done	Renovascular hypertension (right, FMD)
G. B., 59, M	170/110	I	1·0	2966	1·8	0·8	Renovascular hypertension (right, AS)
P. P., 50, F	190/110	II	0·7	5220	1·5	1·0	Renovascular hypertension (right, FMD)
J. O., 59, M	180/92	II	1·7	9905	1·1	1·4	Renovascular hypertension (right, AS)
M. N., 50, F	218/120	II	1·5	4780	2·4	1·2	Renovascular hypertension (left, AS)
S. M., 56, M	194/100	II	1·0	3532	3·6	0·4	Renovascular hypertension (left, AS)
H. H., 53, F	190/100	II	0·8	2618	1·0	2·1	Renovascular hypertension (left, AS)
E. M., 54, F	202/111	III	2·0	9984	3·0	1·4	Renovascular hypertension (bilateral, AS)
A. S., 59, M	170/110	I	1·6	2026	1·2	1·7	Renovascular hypertension (bilateral, AS)
C. D., 51, F	210/110	II	1·0	5640	4·1	0·9	Renovascular hypertension (bilateral, AS)
M. E., 48, F	170/100	II	0·8	2989	1·3	1·3	Renovascular hypertension (bilateral, AS)
N. M., 26, F	144/104	0	0·8	8895	1·0	1·3	Essential hypertension (normal arteriogram)
M. M., 45, F	170/108	II	0·8	8013	1·4	1·0	Essential hypertension (normal arteriogram)
$\bar{X}$ 50	183/107		1·1	5494			
Nonresponders							
B. M., 44, M	190/110	II	1·3	2300	Not done	Not done	Essential hypertension (normal arteriogram)
P. C., 50, F	184/115	0	0·8	1077	Not done	Not done	Essential hypertension
F. G., 57, M	160/100	0	1·1	2262	1·9	0·6	Essential hypertension (normal arteriogram)
B. D., 53, F	188/110	II	0·6	659	Not done	Not done	Essential hypertension
J. S., 49, F	178/104	II	1·0	1428	1·1	1·8	Essential hypertension (incidental stenosis)
E. F., 47, F	190/118	I	1·2	319	Not done	Not done	Essential hypertension
R. E., 47, M	170/114	I	1·0	115	Not done	Not done	Essential hypertension
S. B., 53, M	210/130	II	1·6	134	Not done	Not done	Essential hypertension
$\bar{X}$ 50	184/113		1·1	1037			

* Off medication for 2 weeks.

† Morning of test, after 1 hour of ambulation, furosemide (1 mg/kg) evening before, normal range 673-3155 ng/100 ml/3 hour incubation (95% confidence limits).

‡ FMD, fibromuscular disease; AS, atherosclerosis; incidental stenosis, nonlateralising IVP, renogram/scan, renal vein renin.

Table II

Operations and Blood Pressure Results in 11 Patients with Renovascular Hypertension

Patient	Operation	Result*
M. W.	Autotransplant, right	Cured
G. B.	Aortorenal bypass, right	Cured
P. P.	Aortorenal bypass, right	Cured
J. O.	Nephrectomy, right	Improved
M. N.	Nephrectomy, left	Improved
S. M.	Nephrectomy, left	Cured
H. H.	Aortorenal bypass, left	Cured
E. M.	Nephrectomy, right	Improved
A. S.	Aortorenal bypass, right Nephrectomy, left	Improved
C. D.	Aortorenal bypass, right	Improved
M. E.	Aortorenal bypass, right	Cured

* Average period of follow-up is 10 months. Terms "cured" and "improved" are used as defined in the Cooperative Study of Renovascular Hypertension (Maxwell *et al.*, 1972).

To test the hypothesis that saralasin is a useful tool for the detection of renovascular hypertension in man, the ensuing prospective study was designed, using essential hypertensive patients as controls. This study provides a sizeable experience with saralasin in patients operated on for renal artery stenosis, *i.e.* the diagnosis of renovascular hypertension has been confirmed by post-operative blood pressure results. Moreover, it is the first controlled study where bolus injection of a large dose of the drug has been used in hypertensive man. A portion of this material, dealing primarily with bolus-injection studies, has been presented elsewhere (Marks, Maxwell and Kaufman., 1975). As will be shown, the hypothesis was supported by the results, and a rapid, safe, effective screening procedure was devised.

Patients and Methods

Patients. 10 patients with well-defined essential hypertension and 11 patients with arteriographic evidence of renal artery stenosis were studied. Before entry into the study, the 10 patients with essential hypertension had all exhibited a normal rapid-sequence intravenous pyelogram, a normal renogram/scan, and negative abdominal auscultation for a bruit—a combination which virtually eliminates the possibility of renovascular hypertension (Franklin and Maxwell, 1975). 5 of the patients with essential hypertension also had renal arteriography, which was normal in 4 and showed an incidental stenosis in 1 (Table I).

The 11 patients with renal artery stenosis were all operated upon from one to 30 days following the saralasin study. All 11 patients had technically successful renal revascularisation or nephrectomy with subsequent cure or improvement of hypertension (average follow-up period of 10 months), and they were therefore considered to have renovascular hypertension, as defined in the Cooperative Study of Renovascular Hypertension (Maxwell *et al.*, 1972). The operations and blood pressure results are summarised in Table II.

Groups. At the conclusion of the study, the patients were divided into two groups: "responders" (13 patients) who showed a lowering of blood pressure after receiving saralasin, and "nonresponders" (8 patients) who showed no appreciable lowering of blood pressure after receiving saralasin. Clinical and laboratory characteristics of the two groups are listed in Table I. Statistically, the two groups are matched (*i.e.* they are not significantly different) with respect to age, sex, race (all

Caucasian), hypertensive retinopathy, serum creatinine, and level of blood pressure (Table I). Inasmuch as depressor response to saralasin, when it occurred, was always grossly apparent, assignment into groups was made by visual inspection of the blood pressures plotted before and after saralasin administration.

Saralasin Administration. Each saralasin study was performed in a private room in the UCLA Clinical Research Center.

2 weeks prior to admission, antihypertensive and diuretic medication was discontinued, and a diet of 100-150 mEq/day sodium was begun. On admission, each patient underwent a complete history, physical examination and basic laboratory tests. A consent form, specifically designed for the study and approved in advance by the Human Use Protection and Review Committee of UCLA Medical Center, was signed by all patients. Each study was supervised by the same physician (L. S. M.) and performed by the same two research nurses; the latter were unaware of the patient's diagnosis at the time of the test. Patients with renovascular and essential hypertension were studied randomly throughout the duration of the study.

Saralasin was administered on 2 successive days, the first with the patient ingesting the 100-150 mEq/day sodium diet and the second with the patient in a state of mild salt depletion achieved by administering oral furosemide (approximately 1 mg/kg body weight) the preceding evening. The weight loss caused by the furosemide diuresis was slightly but not significantly greater for the responders than the nonresponders (1·75±0·16 kg SE *versus* 1·56±0·25 kg SE/1·73 m^2 body surface area).

The morning of each test, after the patient's blood pressure was stable in the supine position for at least 30 minutes, a 10-mg bolus of saralasin was hand-injected into the tubing of an indwelling venous catheter. The bolus was given over 2 minutes without the patient's awareness. 30 minutes later, a constant infusion of saralasin (10 mcg/kg/min) was begun. The infusion dose of 10 mcg/kg/min was selected on the basis of dose-response data showing that complete blockade of angiotensin vascular receptor site is achieved at this (or in most cases at a much smaller) dose (Pals *et al.*, 1971; Brunner *et al.*, 1973; Streeten *et al.*, 1976). The infusion was continued for 90 minutes, after which blood pressure was monitored for another 18 hours. Blood pressure was monitored during the study with an automatic blood pressure recorder (Hochberg and Salomon, 1971).

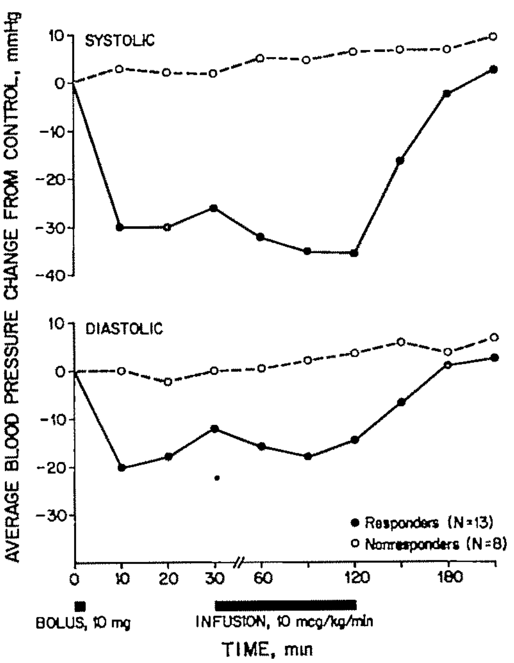

Fig. 2. Average blood pressure changes from control level after saralasin administration. Initial transient (2 to 4 minutes) increase in blood pressure is not shown in figure.

Renin Determinations. Plasma renin activity was determined by radioimmunoassay (Haber *et al.*, 1969), and all samples were run in duplicate.

In our laboratory, this method has a within-assay variation of ±5·6% (Maxwell *et al.*, 1975). Peripheral plasma renin activity, supine and after 1 hour of ambulation, was determined each morning before saralasin was given. For purposes of stratifying the patients into "high", "normal", or "low" renin categories, the ambulatory values after furosemide were used (Table I). The range of normal for this test—673 to 3155 ng/100 ml/3 hour incubation (95% confidence interval)—is based on values obtained in healthy young adults studied previously in our laboratory under conditions identical to those on the second day of saralasin administration (*i.e.* morning collection, 1 hour ambulation, and salt depletion by furosemide).

Samples of renal venous and lower caval blood were obtained for renin assay within 1 month of entry into the study. The samples were obtained with the patient supine, using a single catheter with both side and end holes. Furosemide (approximately 1 mg/kg body weight) was given by mouth the evening before the study. All other antihypertensive medication had been discontinued.

Results

Average blood pressure response to saralasin administration on Day 2 of the study (salt-deplete state) is depicted in Fig. 2. Immediately after the bolus injection of saralasin, all patients in both groups demonstrated a transient (2 to 4 minutes) increase in blood pressure (not shown in Fig. 2). Following this brief pressor phase, the 13 responders demonstrated an average decrease in blood pressure of 30±4·4 SE mm Hg systolic and 20±2·8 mm Hg diastolic at 10 minutes after the bolus injection. The range of decrease in blood pressure was 15 to 55 mm Hg systolic and 10 to 30 mm Hg diastolic for individual responders 10 minutes after the bolus injection. A statistically significant depressor effect persisted thereafter and was maintained throughout the 90-minute infusion ($P<0{\cdot}01$). Blood pressure was lowered to approximately normal levels in all responders except 4 (M. N., H. H., E. M., C. D.) in whom blood pressure was clearly lowered, but not to normal. After the infusion was stopped, blood pressure returned to pre-bolus levels (Fig. 2). During the period of lowered blood pressure, no patient experienced ill-effects or unpleasant sensations. No patient developed tachycardia and none was made hypotensive by the drug.

None of the 8 patients classified as nonresponders showed any measurable depressor effect either after the bolus or during the infusion of saralasin.

On Day 1 of the study (normal salt state), saralasin administration caused no decrease in blood pressure in 6 of the 13 patients who responded to the drug on Day 2 (salt deplete state). The 7 patients who did respond on both days demonstrated a more dramatic decrease in blood pressure on Day 2 than on Day 1. Of the 2 essential hypertensive patients who responded to the drug, one did so on both days (M. M.), while the other responded only on Day 2 (N. M.). All 8 patients classified as nonresponders were nonresponders on both days. As on Day 2, all patients on Day 1 showed a brief pressor effect immediately following the bolus injection.

Among the 13 responders were 11 patients with renovascular hypertension and 2 with essential hypertension (Table I). Both patients with essential hypertension and 7 patients with renovascular hypertension had elevated peripheral renin levels. 4 responders with renovascular hypertension had normal peripheral renin levels. All 8 nonresponders were patients with essential hypertension and normal or low peripheral renin levels. Mean plasma renin activity was significantly higher for the responders than for the nonresponders (5494 ng/100 ml *versus* 1037 ng/100 ml, $P<0{\cdot}01$); however, a partial overlap between the two groups is apparent for individual values (Table I).

Renal vein renin ratios are shown in Table I. Using the criteria of ipsilateral hypersecretion ($I/C \geqq 1{\cdot}5$) and contralateral suppression ($C/IVC < 1{\cdot}3$), this test lateralised the lesion in 7 patients, 6 of whom had renovascular hypertension, and failed to lateralise in 7 patients, 4 of whom (J. O., H. H., A. S., M. E.) had renovascular hypertension and 3 of whom had essential hypertension. 3 patients with renovascular hypertension (H. H., A. S., M. E.) had normal peripheral renin levels *and* nonlateralising renal vein renin ratios: all 3 had depressor responses to saralasin and were subsequently cured or improved by appropriate operations (Table II). 2 of these patients (H. H., A. S.) are discussed in detail elsewhere (Marks *et al.*, 1976).

Discussion

The results obtained in this prospective, controlled study support the hypothesis that angiotensin blockade with saralasin *is* a useful tool for the detection of renovascular hypertension. All 11 patients with renovascular hypertension had clear, unequivocal depressor response to the rapid injection of a saralasin bolus. This effect was sustained during a 90-minute infusion of the drug. A similar depressor response was noted in 2 patients with high-renin essential hypertension, but no such response occurred in 8 patients with normal or low-renin essential hypertension. Thus, if the test were used as a screening procedure for renovascular hypertension, 2 of 13 saralasin responses (15%) were falsely positive, *i.e.* the patients would have been subjected to further investigation before a correct diagnosis became apparent. However, no patient with renovascular hypertension would have been missed, *i.e.* no falsely negative results were obtained.

If the test were considered a screening procedure for *renin-mediated* hypertension, its accuracy in this series was 100%. 4 of 11 responders with renovascular hypertension had normal peripheral renin levels, but in all likelihood their hypertension was renin-mediated. A number of hypotheses would explain how renovascular hypertension may be caused by overactivity of the renin-angiotensin system without absolute elevations in circulating renin levels (Marks *et al.*, 1976). The 20% occurrence of saralasin responsiveness among patients with essential hypertension in this series is in accord with figures given for the prevalence of a high-renin subgroup among the essential hypertensive population (Dunn and Tannen, 1974).

As a predictor of operative results in the patients with renovascular hypertension, response to saralasin compared favourably with renal vein renin determinations. In fact, 4 of 10 patients with renovascular hypertension failed to lateralise a lesion with renal vein renin ratios (falsely negative tests). 3 of these patients also had normal peripheral renin levels, yet all were saralasin responders and operative successes. The problem of falsely negative renal vein renin ratios has been examined previously (Marks and Maxwell, 1975). Response to saralasin may prove helpful in making operative decisions in high-risk patients with hypertension, renal artery stenoses, and nonlateralising renal vein renin ratios (Marks *et al.*, 1976). However, any stronger statement must await operative results in nonresponders; such data are not currently available. A potential source of misleading test results might be a patient with high-renin essential hypertension and an incidental renal artery stenosis. Such a patient did not appear in this series.

Bolus injection of saralasin yielded 10-minute blood pressure results comparable to those obtained during a 90-minute infusion of the drug. Hence, a "Saralasin Bolus Test" was proposed as a simple, rapid screening procedure for renin-mediated hypertension (Marks *et al.*, 1975). To reduce the possibility of falsely negative results, the test is best performed after mild salt depletion. The critical balance between salt and angiotensin was demonstrated in this and other studies where saralasin has been administered before and after salt depletion (Gavras *et al.*, 1973; Donker and Leenen, 1974). After salt depletion, saralasin testing in the *upright* posture will apparently diminish the discriminant value of the test; under these conditions, most patients with essential hypertension will also respond to the drug (Case *et al.*, 1976). Interaction with concomitant antihypertensive drugs is another potential cause of misleading test results or adverse side-effects (Pettinger and Mitchell, 1975). Also, patients who happen to be normotensive at the time of the saralasin administration may not respond to the drug, regardless of the aetiology of their hypertension (Streeten *et al.*, 1975).

The present data add only partial support to a hypothesis of the primacy of the renin-angiotensin system in renovascular hypertension. All patients with renovascular hypertension, when studied under conditions of mild salt depletion (Day 2), did have a clear-cut lowering of blood pressure during angiotensin blockade. However, in 4 of 13 responders, blood pressure was never lowered to entirely normal levels. In addition, in several responders we observed a tendency to escape from the depressor effect toward the latter part of the 90-minute infusion blockade (unpublished data). Thus, some mechanism(s) in addition to direct angiotensin-induced vasoconstriction was responsible for blood pressure elevation in these patients. The data would, therefore, support the recent observation by Macdonald and co-workers that in rats with 2-kidney Goldblatt hypertension, the blood pressure lowering effect of saralasin is not as great as that seen after removal of the clipped kidney (Macdonald, Boyd and Peart, 1975). Whether salt depletion in Macdonald's rats or more extensive salt depletion in our patients would have led to uniform normalisation of blood pressure during angiotensin blockade remains debatable. Resolution of this issue, while important to an understanding of the basic pathophysiology of renovascular hypertension, will not detract from the practical value of saralasin testing as a highly accurate diagnostic procedure.

When viewed from an epidemiologic standpoint, the cost of finding and curing renovascular hypertension—using currently available methods—is enormous. For example, according to one recent report:

> The dollar cost of screening and treating the total American renovascular hypertensive population is of the order of $10 to $13 billion.
>
> Thus . . . some means of selecting patients most likely to benefit from testing and subsequent surgical treatment is necessary (McNeil *et al.*, 1975).

If widespread experience with the saralasin test should confirm its value, as reported here, McNeil's "means of selecting patients" may well be provided. A co-operative study currently in progress should permit a critical evaluation of the test, based on statistical analysis of a large sample.

Summary

Saralasin, a specific competitive inhibitor of angiotensin II, was administered in a controlled, prospective study designed to test the hypothesis that this agent is a useful tool for the detection of renovascular hypertension.

13 patients, 11 with renovascular hypertension and 2 with high-renin essential hypertension, showed a gross, readily apparent decrease in blood pressure after receiving saralasin. 8 patients with essential hypertension and normal or low renin levels exhibited no depressor response to the drug.

In the patients with renovascular hypertension, blood pressure response during angiotensin blockade compared favourably with renal vein renin determinations as a predictor of operative results.

Because saralasin testing has resulted in few if any falsely positive or negative results when considered as a diagnostic procedure for renin-mediated hypertension, and because it is safe, it may become an ideal initial screening procedure.

The saralasin test (either bolus injection or sustained infusion) is completely valid only if the patient is mildly salt-depleted, is not taking other antihypertensive medication, and is genuinely hypertensive at the time of the test.

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The Authors

Leonard S Marks, MD, Resident in Urology.
Morton H. Maxwell, MD, Clinical Professor of Medicine.
Cheryl Cross, RN, Hypertension Research Nurse.
Uzi Waks, MD, Fellow in Nephrology.
Joseph J. Kaufman, MD, Professor of Surgery/Urology.

Requests for reprints: Editor's Office, Department of Surgery, UCLA School of Medicine, Los Angeles, California 90024, USA.

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Studies of Hydrolytic Enzymes and Isoenzymes of Normal and Neoplastic Childhood Renal Tissues and their Tissue Cultured Cells

MADHAV WAGHE and SHANT KUMAR
Clinical Research Laboratories, Christie Hospital, Withington, Manchester, England

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Enzymes and isoenzymes have been shown to exist in different patterns and proportions in various organs (Smith, Perry and Lightstone, 1967; Timperley, Barson and Davies, 1971; Koudstaal, Makkink and Overdiep, 1975; Papiha and Burn, 1976). There are, however, only limited reports on enzyme histochemical studies of childhood kidney tumours and none on the isoenzyme patterns (Elizalde and Miller, 1967; Shimada, 1967).

In this communication we have investigated hydrolases of acid and alkaline phosphatase and non-specific esterases by histochemical and electrophoretic techniques in renal tumours and their cultured cells.

Materials and Methods

Tumour tissue and their normal looking kidneys were obtained within an hour of operation. Samples of normal kidneys at post-mortem and tissue cultured cells of both tumour and normal renal tissue were also used (Table I).

Table I

Source	Investigations Histochemical	 Isoenzymes
Tumour		
Wilms'	24	5
Hypernephroma	1	1
Kidneys		
"Normal looking"	6	3
Adult	8	2
Foetal	2	2
Neonatal	1	1
Tissue culture cells derived from:		
Wilms'	8	–
Hypernephroma	1	–
Normal kidney	2	–
"Normal looking"	4	–

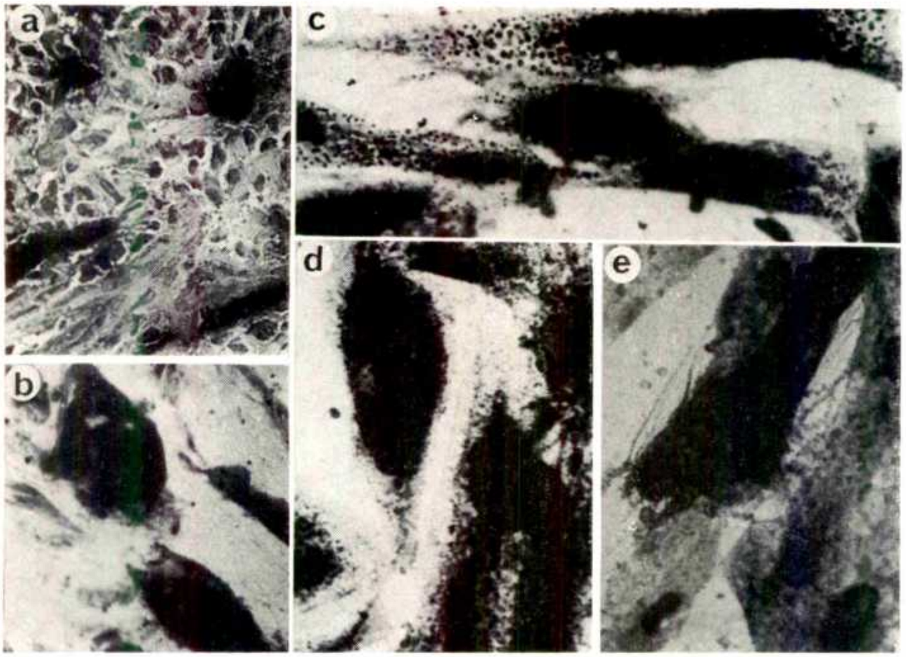

Fig. 1. Cryostat sections of Wilms' tumour showing the presence of (*a*) alkaline phosphatase in blood vessels and (*b*) non-specific esterases in giant cells. Tissue cultured cells derived from Wilms' tumour showing the presence of (*c*) strong staining for non-specific esterase, (*d*) acid phosphatase and (*e*) alkaline phosphatase. × 40.

For histochemical studies 6-8 μ cryostat sections were cut and stained for acid and alkaline phosphatases by the method of Burstone (1958). Non-specific esterases were stained according to Nachlas and Seligman (1949). Cultures of tumours and kidneys were grown on glass coverslips as described earlier (Waghe, Kumar and Steward, 1973). These coverslips with adherent cells were twice washed with phosphate buffered saline and processed in the same way as cryostat sections for staining of the above enzymes. The activity was graded from 0 to 3.

For isoenzyme studies approximately 3 gm of tissue was homogenised with 5 times its volume of phosphate buffered saline pH 7·4. The homogenate was cooled in ice (to avoid overheating) and ultrasonically disintegrated for two 45-second periods with a delay of 2 minutes between each burst. Alkaline phosphatase was extracted from the tissue homogenate with excess of n-butanol (Morton, 1954), and the activity measured by the method described by Kind and King (1954).

Acrylamide Gel Electrophoresis

Samples of extracts were subjected to disc electrophoresis in a Shandon electrophoresis tank (Shandon Scientific Company, London), using a 5% polyacrylamide gel and a continuous buffer system (tris borate buffer pH 9·2). The enzymes were stained by the methods described above.

Alkaline phosphatase was also characterised by other criteria such as heat inactivation (Posen, Neale and Clubb, 1965), urea inhibition (Fennelly, Fitzgerald and McGeeney, 1969) and phenylalanine inhibition (Fishman, Green and Inglis, 1963).

Results

Acid phosphatase and non-specific esterases were present to a certain extent in all tissues examined and their cultured cells (Fig. 1c and d). In general, the enzyme reaction was weaker in differentiated than in undifferentiated tissues. Both the enzymes were particularly active in giant cells (Fig. 1b). The activity was higher in the cells of the hypernephroma than in the Wilms' tumours. In the normal kidney the proximal convoluted tubules showed high activity, the remainder of the tubules moderate activity and the glomeruli weak activity (Table II).

Table II

Enzyme Activity* in Cryostat Sections and Cultured Cells

	Wilms' tumour—cryostat sections (24)				Hypernephroma—cryostat sections (1)					
Enzymes	Differentiated tubules	Undifferentiated tubules	Vessels	Wilms' culture	Tumour cells	Vessels	Reactive	Hypernephroma-culture (1)	Normal kidney—cryostat sections (6)	Normal kidney culture (6)
Acid-PO4	1	2	2	2	3	3	1	2	3	3
Alk. PO4	0	0	3	2	2	3	0	2	3	2
Non Spe. Est.	1	2	2	3	3	3	0	2	3	3

* Enzyme activity was graded from 0 to 3 (0—negative; 1—slight; 2—moderate; 3—strong).
Nos. in parenthesis indicate numbers examined.

Table III

Distribution of Alkaline Phosphatase in Various Tissues

Tumour	Alkaline phosphatase KA units/100 ml of extract supernatant
Wilms' A	3·1
Wilms' B	12·5
Hypernephroma	30·2
Normal kidney	38·0

Alkaline phosphatase was present in high concentration in the cells of the hypernephroma and in the proximal convoluted tubules of the normal kidney. No activity was seen in Wilms' tumours, even in the area of tubular differentiation but their cultured cells showed moderate activity (Fig. 1e). There was strong activity in the blood vessels of the Wilms' tumour, hypernephroma and normal kidney (Fig. 1a).

There was a considerable variation in the amount of alkaline phophatase extracted from the various tissues (Table III). The enzyme of both the Wilms' tumours and the hypernephroma were very sensitive to heat (Fig. 2b), and resistant to L-phenylalanine. The enzyme of normal kidney was slightly less sensitive to heat and was also resistant to L-phenylalanine. Alkaline phosphatase extracted from renal tissues (normal kidney, Wilms' tumour and hypernephroma), was very sensitive to the action of IM urea (Fig. 2a). From the same figure it can be seen that normal serum alkaline phosphatase is considerably less sensitive to urea and heat than that of the other tissues examined.

Electrophoretically, Wilms' tumours showed 1 band of alkaline phosphatase activity. A similar band was also seen in the hypernephroma and in the normal kidneys (Fig. 3b). The hypernephroma showed a second slower moving band which was also present in the normal kidneys. A third thin fast moving band was only present in the normal kidneys.

Only 1 band of acid phosphatase activity was found in all tissues examined and this band was constant in position.

With regard to non-specific esterase the pattern was more complex (Fig. 3a). 7 bands were seen in all normal kidneys (foetal, neonatal, adult and normal looking) and in the hypernephroma. The

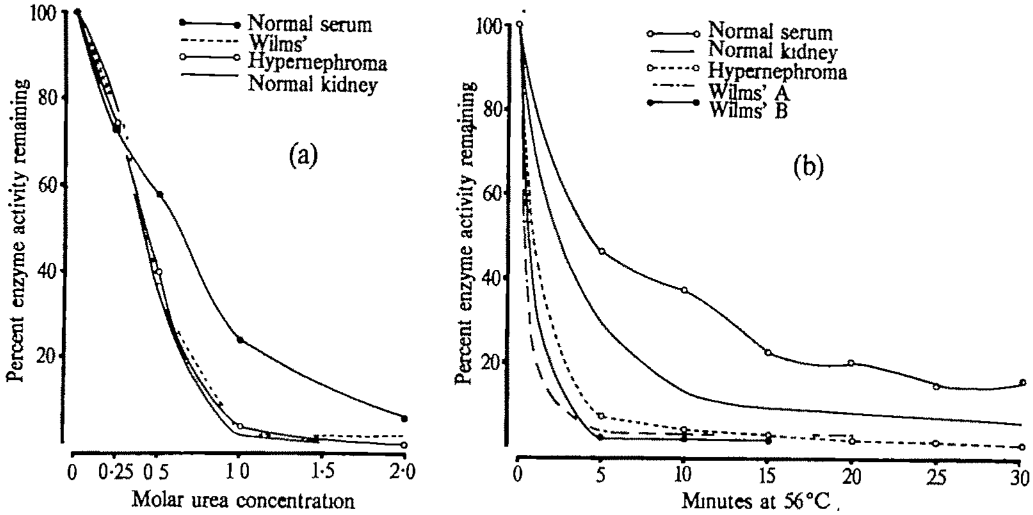

Fig. 2. Effect of urea (*a*) and heat treatment (*b*) on various forms of alkaline phosphatases extracted from normal and neoplastic renal tissues.

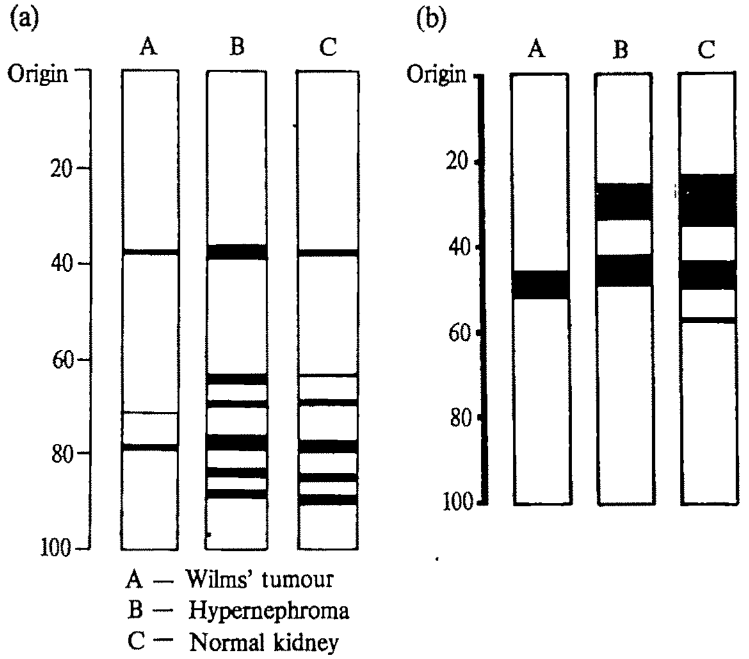

Fig. 3. Electrophoretic patterns of isoenzymes of non-specific esterases (*a*) and alkaline phosphatases (*b*) in normal and neoplastic renal tissues.

Wilms' tumours, however, showed 3 main bands. The other 4 bands seen in the hypernephroma and the normal kidneys were missing.

Discussion

A distinct tumour specific pattern of non-specific esterases was demonstrated in Wilms' tumours. There were 3 bands (isoenzymes) as compared to 7 bands in normal kidneys (foetal, neonatal, adult and normal looking) and hypernephroma. In accordance with our findings Paul and Fottrell (1961) have also described a similar pattern of non-specific esterases in both human foetal and adult kidney. Blanco and Zinkham (1966), however, reported an increase both in the number of isoenzymes and their activities during the development of kidney. One of the reasons for this discrepancy may be that the above studies were not done under identical conditions, and Papiha and Burn (1976) have pointed out that by varying the quantity of a sample and by prolonging the electrophoresis time, the distinction between isoenzymes pattern of adult and foetal brain extracts can easily be distorted.

The presence of a single band of acid phosphatase in tumours and normal kidneys suggests that a common function is performed by it in both normal and neoplastic tissues. Similarly, a single band of acid phosphatase was detected by Estborn and Swedin (1959) in human serum samples.

As regards alkaline phosphatase the activity in Wilms' tumours was either negative or weak, whereas in hypernephroma and normal kidneys it was strong. The blood vessels of all tissues examined including Wilms' tumours were consistently positive. It is interesting that in contrast to the negative activity in cryostat sections of Wilms' tumours their cultured cells had a moderate to strong reaction for alkaline phosphatase. It is possible that the positive cells *in vitro* may have originated from tumour blood vessels rather than tumour cells (Franks and Cooper, 1972).

Electrophoretically, alkaline phosphatase in Wilms' tumours showed a single band which was similar to one of the bands of normal kidney and hypernephroma. This band appears to be the isoenzyme from blood vessels. In the hypernephroma and normal kidneys an additional broad band was seen which was absent in Wilms' tumour. This suggests that it is the isoenzyme of normal renal tissue, which also persists in hypernephroma. The presence of an additional band in normal kidney signifies that this particular component may be a specific form of alkaline phosphatase which is present in normal but not in either Wilms' tumour or hypernephroma.

Summary

The hydrolases of acid and alkaline phosphatase and non-specific esterases were investigated by histochemical and electrophoretic techniques in normal and neoplastic renal tissues and their cultured cells.

A distinct tumour specific pattern of non-specific esterases was demonstrated in Wilms' tumour.

The reasons for the quantitative differences found in the distribution of alkaline phosphatase in Wilms' tumour and their cultured cells are discussed.

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The Authors

Madhav Waghe, BVSc, PhD, Research Fellow (now at Dept. of Safety of Medicine, I.C.I. Ltd, Pharmaceuticals Division, Mereside, Alderley Park, Macclesfield, Cheshire).

Shant Kumar, MVSc, PhD, Head, Tissue Culture and Immunology Department, Christie Hospital, Manchester.

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Renography in the Assessment of Patients with Uretero-sigmoid Diversion

KENNETH S. WILSON, ANDREW DOIG and JAMES W. FOWLER
University Department of Medicine and Department of Urological Surgery, Royal Infirmary, Edinburgh

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The detection of ureteric obstruction and altered renal function forms an important part of the follow-up assessment of patients who have undergone urinary diversion procedures. Soloway *et al.* (1972) have established the value of radio-isotope renography after ileal conduit diversion, but there are no published reports on the evaluation of renography following uretero-sigmoid anastomosis. Whilst urinary diversion after cystectomy is most often established via an ileal conduit, uretero-sigmoid anastomosis is used in patients who will not accept an external stoma and it is also employed by some surgeons in preference to an ileal conduit. In this paper we compare the results of renography and excretion urography in the assessment of separate kidney function after cystectomy and uretero-sigmoid anastomosis for bladder carcinoma; in two-thirds of the patients preoperative comparisons were also made.

Patients and Methods

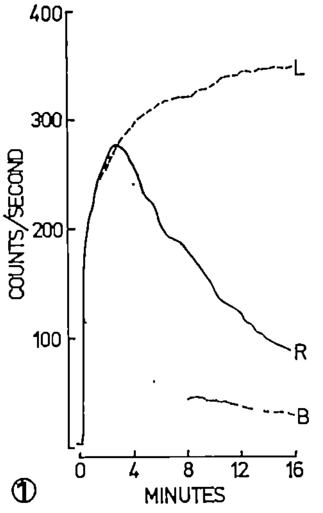
Studies were performed on 26 male and 9 female patients with uretero-sigmoid anastomoses; their mean ages were 59 and 57 years respectively.

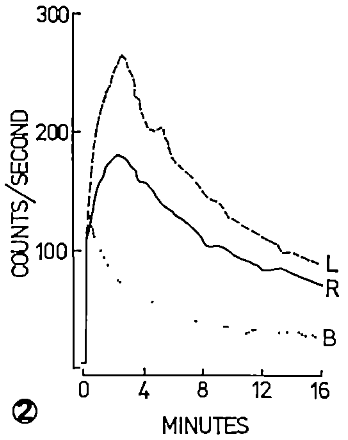
Table

Comparison of Excretion Urogram and Radio-isotope Renogram Findings in the Individual Kidneys of 35 Patients with Bilateral Uretero-sigmoid Anastomoses. Total number of urogram/renogram assessments performed preoperatively (preop.) = 21; and postoperatively (postop.) = 69

		Radio-isotope renogram			
Excretion urogram		Normal	Delayed excretion	Impaired secretory function	Non-function
Normal preop	25	23	1	1	–
Normal postop.	61	36	7	18	–
Hydro-ureter alone preop.	3	–	2	1	–
Hydro-ureter alone postop.	13	7	3	3	–
Hydro-ureter and Hydronephrosis preop.	8	–	8	–	–
postop.	47	–	36	11	–
Poor function preop.	3	–	–	3	–
Poor function postop.	7	–	1	6	–
Non-function preop.	3	–	–	–	3
Non-function postop.	10	–	1	1	8

Dominant abnormality alone is recorded when excretion urogram or renogram showed more than one abnormality.





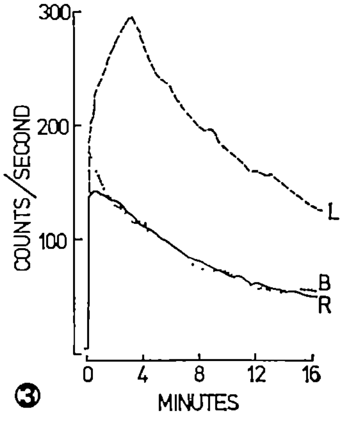


Fig. 1. Postoperative renogram showing marked delay in excretion on left (L) and normal tracing on right (R). Blood background curve (B) is also shown. Excretion urogram was normal.

Fig. 2. Postoperative renogram showing impaired secretory function on right and normal tracing on left. Excretion urogram demonstrated clubbing of middle minor calyces in right kidney.

Fig. 3. Postoperative renogram showing appearances of non-functioning right kidney (right tracing similar in shape to blood background curve) and normally functioning left kidney.

They were assessed by single film excretion urograms taken 20 minutes after the injection of contrast medium and by ^{131}I-ortho-iodohippurate (Hippuran) renography; not more than 28 days elapsed between the 2 investigations. This paired assessment was made on 1 or more occasions in each patient from 14 days to 10 years after the operation. In 21 of the cases preoperative renograms and excretion urograms were also available for comparison.

Renography was carried out without special preparation of the patient apart from ensuring adequate hydration.

3 scintillation counters (5 cm diameter × 5 cm thick thallium iodide activated crystals with 5 cm straight-bore collimators) were used, each connected to a rate-meter and chart recorder. With the patient sitting, 2 counters were placed over the posterior surface markings of the kidneys and the third was positioned over the heart. After the intravenous injection of ^{131}I-Hippuran (10-15 μCi) recordings were made for 20-30 minutes over the areas of maximal counting rate. The tracings from each kidney were evaluated by visual inspection for evidence of impaired secretory function and delayed excretion (Lawrence *et al.*, 1963; Maxwell and Hayes, 1972).

Results

The results are summarised in the table and examples of the abnormalities found on renography are shown in Figs 1-3. In the preoperative assessment, a good correlation was obtained between normal findings in the excretion urogram and renogram, whereas after operation, 25 renograms showed abnormalities in the presence of a normal excretion urogram, the majority consisting of minor degrees of impairment in secretory function; however, in 2 of the 7 cases showing a delay in excretion, radiological evidence of hydronephrosis subsequently appeared. Hydro-ureter without hydronephrosis was demonstrated radiologically in 15 instances; the renogram tracing from 7 of these kidneys was normal and in this subgroup later excretion urograms revealed disappearance of the hydro-ureter in 5 and no change in 2.

In hydronephrosis associated with hydro-ureter there was close agreement between the renogram and excretion urogram findings, the dominant renographic abnormality in most instances being a marked delay in the excretory phase; in those tracings in which impaired secretory function was the main abnormality a delay in excretion usually co-existed. There was also close agreement between the results of the 2 investigations in kidneys with poor or absent function. In the 2 cases where there was evidence of secretory function in the renogram but none in the excretion urogram the degree of functional impairment was severe.

Discussion

Whilst routine measurements of plasma urea and electrolytes will reveal most of the biochemical disturbances which occur after uretero-sigmoid anastomosis, they fail to show early evidence of progressive deterioration in renal function at a stage when further surgical measures may be of value. Periodic excretion urography is therefore used after urinary diversion procedures to assess separate kidney function and to detect out-flow tract abnormalities.

In this study of patients with uretero-sigmoid anastomosis we have employed radio-isotope renography in the assessment of individual kidney function and have compared the findings with those of excretion urography. Whereas a good correlation was found between the results of the 2 investigations before operation, close agreement only obtained after the urinary diversion when the excretion urogram showed hydronephrosis or poor or absent kidney function.

Almost half the normal excretion urograms after operation were associated with renograms which showed evidence of impaired secretory function or delayed excretion. Although most of these abnormalities were mild they could not be dismissed without further follow-up as a few increased in severity and became associated with frank radiographic evidence of renal impairment or hydronephrosis. The lesser degree of correlation of the findings in this group was not unexpected as it is recognised that radio-isotope renography provides a better evaluation of kidney function than excretion urography (Joekes, 1972).

A further discrepancy in the results after operation was the occurrence of a normal renogram in association with half the excretion urograms showing hydro-ureter as an isolated abnormality. Absence of functional evidence of obstruction suggests that the ureteric dilatation resulted from reflux or from ureteric obstruction which had undergone spontaneous relief; subsequent excretion urograms in most instances showed disappearance of the hydro-ureter and in none was there progression to hydronephrosis. The good prognostic significance of ureteric dilatation with a normal renogram has previously been discussed by Wax and McDonald (1966).

We conclude from our findings that the long-term follow-up of patients with uretero-sigmoid diversion can be efficiently supervised by periodic renograms, plain abdominal X-rays and routine blood chemistry, with restriction of excretion urography to patients who show significant or progressive changes in these tests. Relative to the current practice of review by serial excretion urography and blood chemistry, this scheme offers earlier detection of alterations in kidney function and ureteric obstruction and the additional advantages of a lesser radiation hazard, decreased cost and greater patient acceptability.

Summary

A comparison was made between the excretion urogram and the radio-isotope renogram in 35 patients with uretero-sigmoid anastomosis. A good correlation was obtained between the 2 tests in the presence of radiographic evidence of (*a*) hydronephrosis, (*b*) poor renal function and (*c*) absent function.

Renographic evidence of mild impairment of secretory function and of delayed excretion was associated with a significant number of normal excretion urograms and in a few instances there was later progression to severe renal impairment or hydronephrosis.

Hydro-ureter associated with a normal renogram carried a good functional prognosis.

Renography is recommended in the long-term supervision of patients with uretero-sigmoid anastomosis.

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The Authors

Kenneth S. Wilson, MRCP(UK), Medical Registrar.
Andrew Doig, FRCP, FRCPE, Consultant Physician and Senior Lecturer.
James W. Fowler, FRCSE, Consultant Surgeon.

Correspondence should be sent to Dr K. S. Wilson, Senior Cancer Clinic Associate, Saskatoon Cancer Clinic, University of Saskatoon Hospital, Saskatoon, Saskatchewan, Canada.

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Glomerulosclerosis following Irradiation and Cytotoxic Therapy for Nephroblastoma

A.A.M. GIBSON, A.A. BUSUTTIL, D.G. YOUNG and G. E. FLATMAN

Departments of Pathology and Paediatric Surgery, Royal Hospital for Sick Children, Glasgow, and the Glasgow Institute of Radiotherapeutics, Western Infirmary, Glasgow

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Acute radiation nephritis is a well-documented but fortunately rare complication of abdominal irradiation for nephroblastoma. The clinical and pathological features of acute and chronic forms of radiation nephritis have been described by Luxton and Baker (1968). Relatively little is known about latent or subclinical damage to the kidneys. This paper concerns a boy who died of metastatic tumour 13 months after diagnosis of a nephroblastoma. He received irradiation and cytotoxic therapy after nephrectomy. There was diffuse mesangial glomerulosclerosis in the remaining kidney at necropsy. This lesion is attributed to postoperative irradiation and cytotoxic therapy.

Case Report

A previously healthy 6-year-old boy was admitted to hospital with a 2-month history of listlessness, anorexia and loss of weight. His mother had noticed swelling of his abdomen for the last 4 weeks. 4 days prior to admission he developed left-sided abdominal pain with vomiting. On examination he was an ill child with a large firm abdominal mass mainly on the left side but extending across the midline. He was mildly anaemic (Hb 9·2 g/100 ml) and the E.S.R. was 120 mm in the first hour. The blood pressure was normal. There was neither protein nor any microscopic abnormality in the urine. An intravenous pyelogram showed a normal right pyelogram but distortion of the left renal pelvis and calyces indicative of a nephroblastoma; chest X-ray was normal. Laparotomy was performed on the day after admission. The left kidney with the tumour was excised as were para-aortic and coeliac lymph nodes. The kidney was largely replaced by a mass of necrotic and haemorrhagic tumour which proved to be a poorly differentiated nephroblastoma. The surviving renal parenchyma showed no significant abnormality. All of the excised lymph nodes were infiltrated by tumour.

The additional therapy and clinical course related to the date of operation were as follows:

Days 0-4.	Actinomycin D 15 μg/kg intravenously (i.v.) daily.
Days 14-42.	Abdominal irradiation by linear accelerator using parallel opposed fields to a tumour dose of 3,000 rads in 10 treatments to each field. The right kidney was shielded after a dose of 1,500 rads.
8 weeks.	Laparotomy for intestinal obstruction with release of postoperative adhesions. Pulmonary metastases detected on X-ray.
11-15 weeks.	Radiotherapy to the chest by means of the linear accelerator. A tumour dose of 1,500 rads was delivered by means of anterior and posterior parallel opposed fields over a period of 25 days. The right renal area was not included in the fields.
16-21 weeks.	Vincristine, 1·5 mg/m^2 i.v. weekly.
22-54 weeks.	Vincristine, 1·5 mg/m^2 i.v. on alternate weeks.
55 weeks.	Re-admitted to hospital with signs of extensive metastases in the right lung and chest. Normal blood pressure. Actinomycin D 15 μg/kg i.v. daily for 5 days.
56 weeks.	Steady deterioration and death.

Necropsy Findings. The tumour had spread to the deep cervical and mediastinal lymph nodes, the right pleural cavity and both lungs. There was a local recurrence in the left renal bed. The right kidney (weight 200 g) showed compensatory hypertrophy. On histological examination throughout the kidney there was a diffuse glomerular lesion with a variable degree of mesangial hypercellularity and deposition of mesangial matrix (Fig. 1 A and B) generally affecting the whole tuft. Occasional tufts showed lobular necrosis. The mesangial matrix was hyaline and

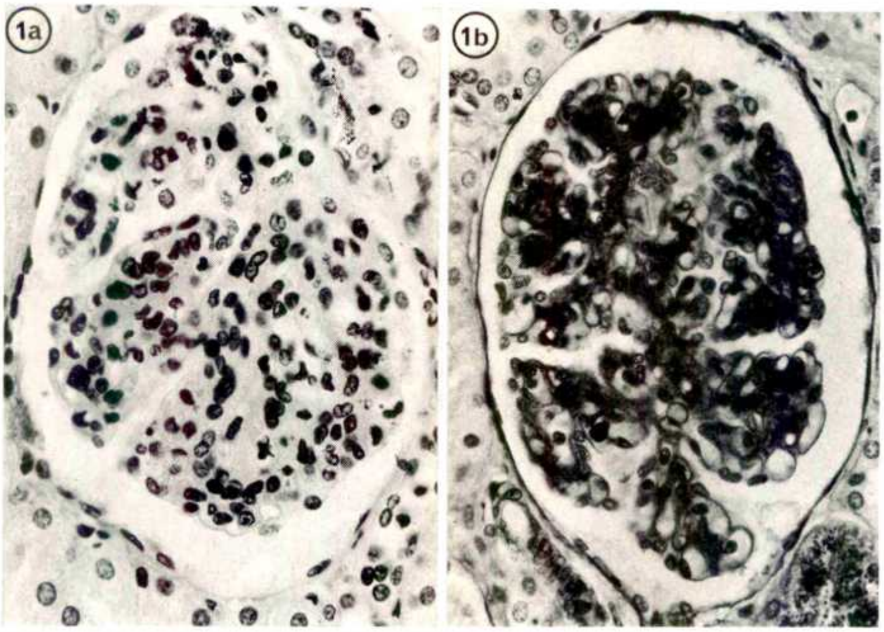

Fig. 1. A, A glomerulus showing mesangial hypercellularity. Haematoxylin and eosin. × 400. B, A glomerulus showing increased mesangial matrix. Periodic acid Schiff. × 400.

eosinophilic, stained strongly by the periodic acid Schiff (PAS) technique in a slightly fibrillary manner and uniformly blue with Lendrum's martius scarlet blue stain. Amyloid was not demonstrated. Similar material was present in the wall of a few afferent arterioles and small arteries. There was no evidence of necrosis in the arterioles. The large blood vessels were normal. Epithelial crescents were not present in Bowman's space. Hyaline protein droplets were seen occasionally in the visceral epithelial cells of the glomeruli but they were more prominent in the proximal convoluted tubules. There were a few protein casts in the distal tubules and occasional atrophic tubules with thickened basement membrane. A very scanty interstitial lymphocytic infiltrate was noted but interstitial oedema and fibrosis were absent. A review of the left nephrectomy specimen confirmed that the surviving renal parenchyma was normal histologically.

Discussion

The evidence that the renal lesion demonstrated at necropsy is related to the postoperative therapy in this case is circumstantial. Although renal function was not investigated before the nephrectomy, the child was normotensive and there was no proteinuria or haematuria. Intravenous urography and histology of the nephrectomy specimen also exclude any significant pre-existing renal disease apart from the tumour.

The renal pathology does not suggest either acute or chronic radiation nephritis. Unfortunately little is known about the pathology in the subclinical cases; a renal biopsy is reported in a patient with asymptomatic proteinuria, (Luxton and Baker, 1968). Glomerular changes similar to those found in the present case are described but arterial and arteriolar hyalinisation is emphasised.

Nephrotoxicity has not been described with either actinomycin D or vincristine therapy alone. The possibility of these drugs potentiating the effect of the irradiation must be considered. There is clinical and experimental evidence for an enhanced effect of irradiation on the skin by either concurrent or subsequent administration of actinomycin D (D'Angio, Farber and Maddock, 1959). Previous studies in adults have indicated that overt radiation nephritis is liable to develop only when the dose exceeds 2,300 rads (Kunkler, Farr and Luxton, 1952). The right kidney received 1,500 rads, half of the total dose to the abdomen. There is now a considerable experience with this schedule of radiotherapy, either alone or combined with actinomycin D, and glomerulosclerosis has not been described previously in the surviving kidney. Hepatotoxicity and cardiotoxicity have been reported where these organs have been subjected to combined therapy by irradiation and cytotoxic drugs (McVeagh and Ekert, 1975; Gerber, Gilbert and Chung, 1975). If the renal lesion is indeed a complication of therapy the addition of vincristine must be implicated. 2 other surviving children who received a combination of irradiation, actinomycin D and vincristine for nephroblastoma have shown clinical features of nephritis (Arneil *et al.*, 1974). This suggests that the radiosensitivity of the kidney may be increased by cytotoxic therapy, particularly with combinations of drugs, and emphasises the importance in these circumstances of screening the remaining kidney throughout the postoperative irradiation.

Summary

A 6-year-old child had a nephrectomy for nephroblastoma followed by radiotherapy and chemotherapy with actinomycin D and vincristine.

He died of metastatic disease 13 months after the operation.

Autopsy showed a diffuse glomerulosclerosis in the remaining kidney which is attributed to the postoperative therapy.

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The Authors

A. A. M. Gibson, FRCP(Ed), MRCPath, Consultant Pathologist.
A. A. Busuttil, MD, MRCPath, Lecturer in Pathology.
D. G. Young, FRCS(Ed and Glasg), Senior Lecturer in Paediatric Surgery.
G. E. Flatman, MD, FRCS, FFR, Deputy Director Glasgow Institute of Radiotherapeutics.

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Short Case Report

Transitional Cell Carcinoma of the Renal Pelvis presenting with Peripheral Neuropathy

A 54-year-old man presented with a 5-week history of paraesthesia of the fingers and toes and a sensation of walking on cotton wool. He admitted to passing "dark coloured urine" intermittently for 5 years. In 1968 he had undergone a successful resection of a well-differentiated adenocarcinoma of the transverse colon.

Examination revealed a fit man with a slow and unsteady gait. He had absent reflexes and altered sensation to pinprick and light touch in the fingers and lower limbs. The urine contained blood. An IV urogram showed a non-functioning right kidney and selective right renal angiography demonstrated a papillary lesion of the renal pelvis (Fig.). A chest X-ray was normal.

He underwent a right nephro-ureterectomy and made an uneventful recovery. His paraesthesiae had disappeared by the end of the first post-operative week, and when examined 3 months after surgery, there was no demonstrable sensory deficit, and his reflexes had returned to normal. Histology showed the tumour to be a moderately differentiated transitional cell carcinoma.

Comment

Peripheral neuropathy is a well-documented complication of malignant disease and, in particular, carcinoma of the bronchus (Croft and Wilkinson, 1965). It has been described as a non-metastatic complication of many tumours (Croft, Ulrick and Wilkinson, 1967), but not in association with urothelial cancer. In this case the neuropathy completely disappeared after removal of the tumour.

We wish to thank Dr I. M. S. Wilkinson for his advice on this case.

D. P. Fawcett and M. P. McBrien
West Suffolk Hospital, Bury St Edmunds

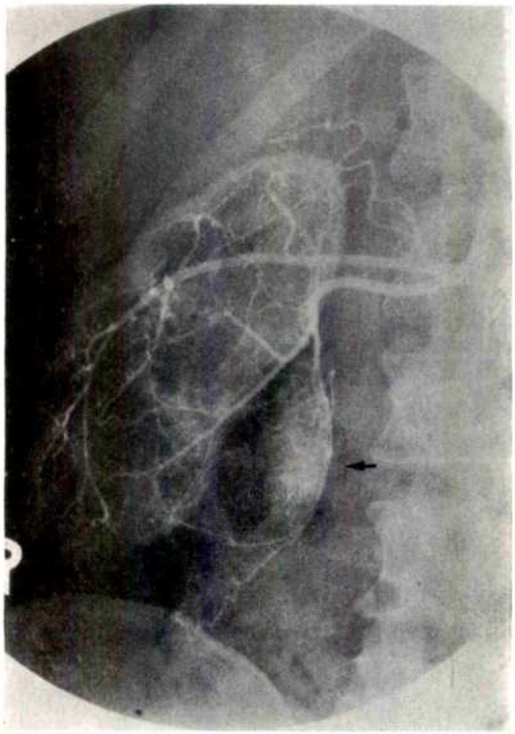

Fig. Selective (R) renal angiogram showing papillary tumour of the renal pelvis (arrowed).

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The Behaviour of the Ureters following Radiotherapy and Wertheim Hysterectomy

J. STUART TAYLOR
Royal Newcastle Hospital, Newcastle, N.S.W., Australia

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The insertion of radium followed by Wertheim hysterectomy is a frequently performed procedure for carcinoma of the cervix of the uterus. Subsequently, dilatation of the upper two-thirds of the ureters commonly occurs. This dilatation usually disappears within 6 months, and does not have clinical or prognostic significance. This paper presents the results of a study of these changes.

Patients and Prodecures

19 cases were studied, 11 retrospectively and 8 prospectively. The investigation protocol was as follows: (1) Full physical examination before surgery, and at the time of the radiological studies after surgery. (2) Intravenous urogram prior to surgery. (3) Intravenous urogram or retrograde pyelogram with a study of the ureteric behaviour under image intensification, with appropriate spot films, 6 months or more after surgery. In addition, all the patients in the prospective group had an intravenous urogram or retrograde pyelogram with studies under the image intensifier done 4 to 6 weeks after surgery. (4) Transrectal Frantzen needle biopsy of any cases in which the suspicion of recurrence of malignancy was raised.

Results

These are most clearly seen when the cases are divided into 2 groups—the retrospective group, and the prospective group.

Retrospective Group (Table I). All 11 cases had a normal intravenous urogram preoperatively. At the postoperative check 6 or more months after operation 6 patients had normal physical examination, normal intravenous urogram, and under the image intensifier the ureteric dynamics appeared normal.

In the remaining 5, abnormalities were present.

Table I

Retrospective Group

Total number	11
Normal findings	6
Normal radiographic findings but recurrence in pelvis	1
Hydroureter alone	2
Hydroureter and hydronephrosis	2

Table II

Prospective Group

Total number	8
At 4-6 weeks:	
Normal	2
Ureteric dilatation	6
At 6 months:	
Normal	6
Clinical recurrence with normal radiographic findings	1
Ureteric dilatation but no recurrence	1

Of these 5 patients, 2 had slight dilatation of the middle third of the ureters. In these patients, image intensifier studies showed obliterative peristaltic waves passing the full length of each ureter. However, dye tended to pool in the dilated middle third of the ureter for an unusual length of time, and then was transmitted unusually rapidly across the lower one-third of the ureters into the bladder. In these 2 patients with this slight dilatation physical examination was normal in each case.

Another of these 5 patients had marked bilateral ureteric dilatation of all but the lower 6 cm of each ureter, with dilatation of the renal pelves and calyces. Physical examination in this case was normal. Rectal examination revealed the smooth fan of tissue characteristically felt following Wertheim hysterectomy with no suggestion of malignancy. Transrectal Frantzen needle aspiration with exfoliative cytology studies showed no malignant cells. The lower third of each ureter was dilated to size 10 Charriere, and follow-up intravenous urogram at 3 months showed marked reduction in the degree of dilatation of the ureters. A further intravenous urogram 12 months later showed that this improvement was being maintained.

Another of these 5 patients showed gross unilateral hydronephrosis and a hydroureter throughout all but the lower 3 cm of that ureter. This patient had developed a uretero-vaginal fistula 2 weeks after operation. Rectal examination revealed a craggy irregularity in the post-Wertheim fan. Frantzen needle aspiration with exfoliative cytology showed malignant cells in the smears. Ureteric reimplantation cured the fistula, and the ureteric dilatation returned to normal. Open biopsy at the time of ureteric reimplantation confirmed the presence of malignancy from the previous carcinoma of the cervix of the uterus. This patient subsequently died with extensive metastases.

Another of these 5 patients had a normal postoperative intravenous urogram and normal ureteric dynamics. Rectal examination revealed an irregular hard mass in the post-Wertheim fan. Frantzen needle aspiration revealed malignant cells. This patient is still alive, but recurrence is now even more extensive, and has been confirmed by biopsy and histological examination.

Prospective Group (Table II). All of these patients had normal intravenous urograms pre-operatively. It should be noted that only those patients with normal pre-operative intravenous urograms were subjected to this form of treatment. The results are remarkably similar to those in the retrospective group, but the early postoperative urograms demonstrated an interesting phenomenon: in 6 of the 8 cases there was mild dilatation of the middle and upper thirds of both ureters 4 to 6 weeks after surgery. Study of the dynamics of these ureters under image intensification showed somewhat sluggish ureteric activity in the dilated section, although obliterative peristaltic waves did occur. Again the dye tended to hang in the dilated portions of the ureters, and in contrast to this sluggishness, transit across the lower undilated section was unduly rapid. In 5 of these 6 cases this appearance had reverted to normal in the intravenous urogram studies at 6 months. In the other case considerable improvement had occurred in one ureter, but little improvement in the other.

Of the 2 remaining cases in this group, 1 case developed a uretero-vaginal fistula, but without tumour recurrence. The intravenous urogram showed the typical hydroureter of this condition, and this was again cured by ureteric reimplantation.

The other case showed the development of an irregular mass in the post-Wertheim fan upon rectal examination at 6 months. Intravenous urogram revealed normal urinary tracts without ureteric dilatation. Frantzen needle aspiration biopsy with cytological examination revealed malignant cells, and this finding was subsequently confirmed by biopsy and histological examination.

Discussion and Conclusion

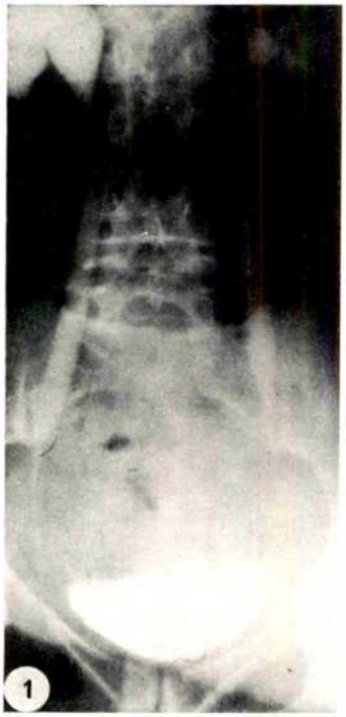
In the early months following radiotherapy and Wertheim hysterectomy, the ureters usually show a moderate degree of dilation of their upper two-thirds, with occasional hydronephrosis. The urine tends to hang in this dilated portion of the ureters, and be transmitted very rapidly across the undilated lower portion (Fig. 1). By the time 6 months have elapsed this dilatation has disappeared in most cases, although occasionally slight dilatation of the middle third may persist (Fig. 2). Very rarely this dilatation may be more severe, with accompanying hydronephrosis.

This ureteric dilatation is of no value in itself in determining whether tumour recurrence is present or not. This paper presents cases in which ureteric dilatation was present, but tumour recurrence was not, and in which no ureteric dilatation was present, but tumour recurrence was.

In the absence of tumour the more severe degree of ureteric dilatation has been shown to respond to simple ureteric dilatation.

Rectal examination is of the greatest help in assessing whether tumour recurrence is present. Normally after radiotherapy and Wertheim hysterectomy, rectal examination reveals a smooth but very firm fan of tissue that commences postero-laterally on the pelvic wall on either side, sweeps forward following the course the removed utero-sacral ligaments followed, and then medially across the back of the bladder at the level of, or slightly above the inter-ureteric bar. The smooth, very firm feel of this fan is quite characteristic, and the development of irregularity in it should be viewed with great suspicion.

If the situation is in doubt, Frantzen needle aspiration with cytological examination is of great



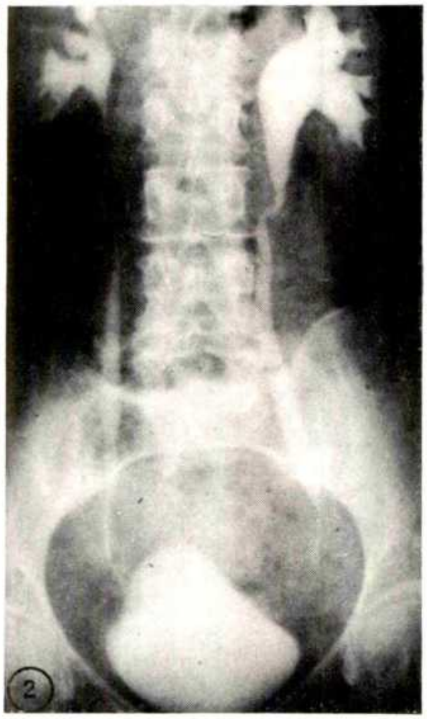


Fig. 1. IVP 6 weeks after Wertheim hysterectomy showing dilatation of lumbar segments of ureters.

Fig. 2. IVP 6 months after Wertheim hysterectomy showing slight residual dilation of ureters.

value. It is a simple procedure to perform, and does not appear to have any morbidity. In this series it has not produced any false negative or false positive results.

Summary

The pyelographic appearances following Wertheim hysterectomy have been studied in 19 cases.

The dilatation of the lumbar segments with unusually rapid transmission through the pelvic segments has been found 6 weeks postoperatively although this dilatation has disappeared in most cases by 6 months.

Late ureteric dilatation is of no value in itself in determining the presence or absence of recurrent growth.

The Author

J. Stuart Taylor, FRCS, FRCSE, FRACS, Urologist.

Address for correspondence: 108 King Street, Newcastle 2300, N.S.W., Australia.

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Second Report on the Standardisation of Terminology of Lower Urinary Tract Function

PRODUCED BY THE INTERNATIONAL CONTINENCE SOCIETY, AUGUST 1976

Members: Patrick Bates, Eric Glen, Derek Griffiths, Hansjorg Melchior, David Rowan, Arthur Sterling, Norman Zinner, Tage Hald (Chairman)

Introduction

This report contains the second set of recommendations dealing with the terminology of lower urinary tract function. It covers micturition and recommendations for the use of symbols. The recommendations were subject to discussion during the Fifth Annual Meeting of the International Continence Society in Glasgow, Scotland, September 1975.

These standards are proposed to facilitate comparison of results by investigators who use urodynamic methods. It is recommended that the acknowledgement of these standards in written publications be indicated by a footnote to the section "Methods and Material" or its equivalent:

> "Methods, definitions, and units conform to the standards proposed by the International Continence Society except where specifically noted."

Urodynamics encompasses the morphological, physiological, biomechanical and hydrodynamic aspects of urine transport. This report deals with the urodynamics of the lower urinary tract.

Procedures Related to the Evaluation of Micturition

Flow rate

Flow rate is defined as the volume of fluid expelled via the urethra per unit time. It is expressed in ml/s.

Specify:
1. Patient environment and position: (1) supine
   - (2) sitting
   - (3) standing.
2. Filling: (1) by diuresis: (i) spontaneous
   - (ii) forced (specify regimen)
   - (2) by catheter: (i) transurethral } state rate.
   - (ii) suprapubic } state rate.
3. Fluid—indicate temperature.

Technique:
1. Measuring equipment.
2. Solitary procedure or combined with other measurements.

Definitions:
1. *Continuous flow* (see Fig. 1).
   Flow time is the time over which measurable flow actually occurs.
   Time to Maximum flow is the elapsed time from onset of flow to maximum flow.
   Maximum flow rate is the maximum measured value of the flow rate.
   Voided volume is the total volume expelled via the urethra.
   Average flow rate is voided volume divided by flow time.

Revised following discussion during the business meeting of the International Continence Society, Antwerp, September 1976.

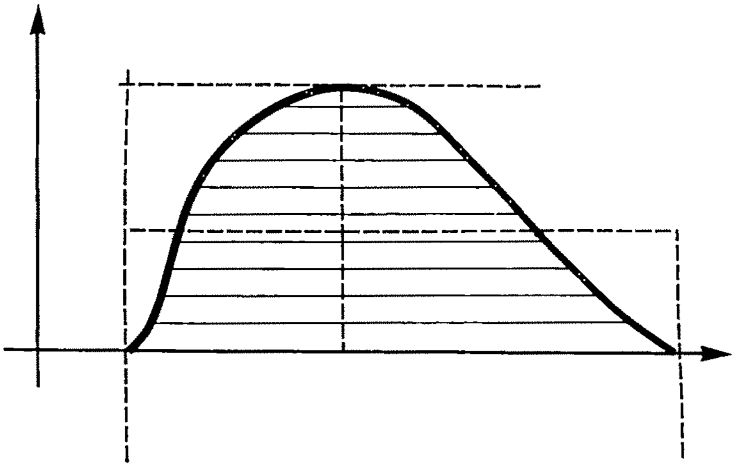

Fig. 1. Diagram of continuous flow curve.

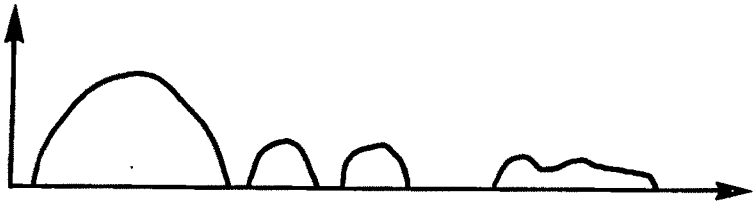

Fig. 2. Diagram of intermittent flow curve.

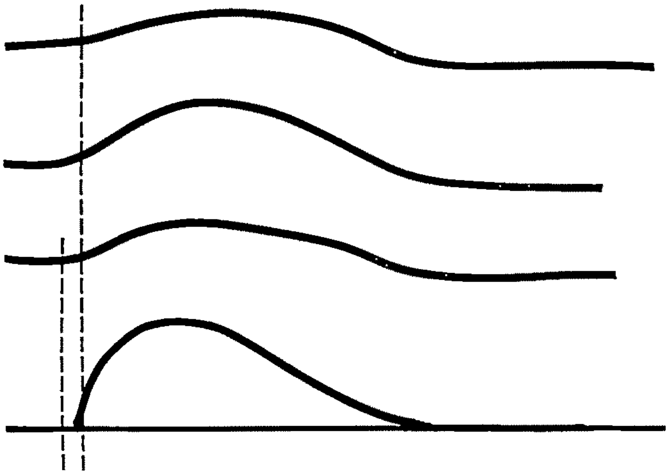

Fig. 3. Diagram of corresponding pressures and curve of flow. The order of presentation of curves as shown above is recommended.

2. *Intermittent flow or continuous flow with substantial terminal dribbling* (see Fig. 2).
   The same parameters are applicable if care is exercised in measuring flow time as defined above, *i.e.* time intervals between flow episodes are disregarded, or if the duration of very low terminal flow is disregarded.

Voiding time is total duration of micturition, *i.e.* includes interruptions.
In continuous flow situation, voiding time is equal to flow time.

Flow pattern

Specify pattern description. This cannot be defined at present and is best illustrated.

Comment:

Measurement of the flow rate has value
(*a*) as screening procedure
(*b*) in assessing results of treatment
(*c*) in assessing progression of disease.
However, as an isolated measurement it has limitations. In particular it may have to be related to bladder pressure, initial and residual volume in the bladder and of course age and sex.

Pressure Measurements during Micturition

Zero reference for all pressure measurements is the level of the superior edge of the symphysis pubis. Pressures are expressed in cm H_2O.

Specify: Access to intravesical pressure (1) transurethral
(2) suprapubic
(3) telemetry.
Access to abdominal pressure (1) rectal
(2) gastric
(3) intraperitoneal.
Position (1) supine
(2) sitting
(3) standing.

Technique: 1. Catheter type and size.
2. Measuring equipment.

Definitions (see Fig. 3):

Intravesical pressure is the pressure within the bladder.

Abdominal pressure is taken to be the pressure surrounding the bladder. In current practice it is estimated from rectal, gastric or intraperitoneal pressure.

Detrusor pressure is that component of intravesical pressure which is created by forces in the bladder wall (passive and active). It is estimated by subtracting abdominal pressure from intravesical pressure.

Opening time is the elapsed time from initial rise in detrusor pressure to onset of flow. This is the initial isovolumetric contraction period of micturition. Time lags should be taken into account.

The following parameters are applicable to measurements of each of the pressure curves: intravesical, abdominal and detrusor pressure (see Table I):

Premicturition pressure is the pressure recorded immediately before the initial isovolumetric contraction.

Opening pressure is the pressure recorded at the onset of measured flow.

Maximum pressure is the maximum value of the measured pressure.

Pressure at maximum flow is the pressure recorded at maximum measured flow rate.

Contraction pressure at maximum flow is the difference between pressure at maximum flow and premicturition pressure.

Postmicturition events are at present not well understood and so cannot be defined.

It is common practice to relate pressure and flow by calculation of a resistance factor. However, caution should be exercised in interpreting this number. The subject of resistance factors will be dealt with in a later report.

Symbols

It is often helpful to use symbols in a communication.

The system below has been devised to standardise a code of symbols for use in urodynamics.

The rationale of the system is to have a basic symbol representing the physical quantity with qualifying subscripts.

The list of basic symbols largely conforms to international usage. The qualifying subscripts relate the basic symbols to commonly used urodynamic parameters (Table II).

Table I

Parameters of Pressure in the Micturition Cycle

	Pressure curves		
	Intravesical	Abdominal	Detrusor
Premicturition pressure	Intravesical premicturition pressure	Abdominal premicturition pressure	Detrusor premicturition pressure
Opening pressure	Intravesical opening pressure	Abdominal opening pressure	Detrusor opening pressure
Maximum pressure	Maximum intravesical pressure	Maximum abdominal pressure	Maximum detrusor pressure
Pressure at maximum flow	Intravesical pressure at maximum flow	Abdominal pressure at maximum flow	Detrusor pressure at maximum flow
Contraction pressure at maximum flow	Intravesical contraction pressure at maximum flow	Abdominal contraction pressure at maximum flow	Detrusor contraction pressure at maximum flow

Table II

List of Symbols

Basic symbols		Urological qualifiers		Value	
Pressure	p	Bladder	ves	Maximum	max
Volume	V	Urethra	ura	Minimum	min
Flow rate	Q	Ureter	ure	Average	ave
Velocity	v	Detrusor	det		
Time	t	Abdomen	abd		
Temperature	T				
Length	l				
Area	A				
Diameter	d	Example:			
Force	F	$p_{ves,\,max}$ = maximum intravesical pressure			
Energy	E				
Power	P				
Compliance	C				
Work	W				

If all parameters were to be given standard symbols the system would be clumsy. If further qualifiers therefore are required they should follow this system and be defined.

This report was supported by grants from the Danish Research Council and P. Carl Petersen's Foundation.

The first report on the standardisation of terminology of lower urinary tract function:
British Journal of Urology (1976), **48**, 39-42.
Urologe A (1976), **15**, 93-96.
Zeitschrift für Urologie und Nephrologie (1976), **69**, 421-426.
European Urology (in press).
Journal d'Urologie et de Nephrologie (Paris). Submitted.
Scandinavian Journal of Urology and Nephrology. Submitted.

British Journal of Urology (1977), 49, 211-214 ©

A Psychiatric Study of Women with Urgency and Urgency Incontinence

R. JULIAN HAFNER, STUART L. STANTON and JOHN GUY

Department of Obstetrics and Gynaecology and Department of Psychiatry, St George's Hospital, London

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The aims of this study are to define the nature and extent of psychological disorder in women with urgency and urgency incontinence in the absence of organic structural bladder and urethral abnormality, and to determine the extent to which the symptoms yield to psychological and behavioural treatments.

Frewen (1972, 1976) has stressed the psychosomatic nature of urgency and urgency incontinence in women. However, he found that 20% of his patients did not improve following simple psychotherapy, bladder training, and medication.

Patients, Design and Methods

31 patients were seen at the Urodynamic Clinic (S.L.S) complaining of frequency, urgency and urgency incontinence. They were aged between 18 and 65 years, were of mixed parity and were otherwise healthy.

Clinical examination and culture of a mid-stream specimen of urine were normal. Cystoscopy and videocystourethrography with pressure and flow studies revealed no structural bladder or urethral abnormality. The patients then underwent psychiatric assessment (R. J. H. and J. G.) and were subsequently offered psychological and later behavioural treatment. As part of the psychiatric assessment, they completed the Middlesex Hospital Questionnaire (MHQ: Crown and Crisp, 1966) the Eysenck Personality Inventory (EPI: Eysenck, 1964) and a Fear Survey Schedule (FSS). These questionnaires reflect aspects of neuroticism and extraversion.

Psychological treatment comprised six 1-hour sessions in groups of 4 to 6, where the patients were taught a modified version of Autogenic Training (Schultz and Luthe, 1959). This procedure aims to enable the individual to learn to acquire greater control of body functions. After 3 such groups, the next 4 suitable referrals were offered individual psychotherapy, to enable a more detailed analysis and treatment of any relevant psychological disorders. 1 patient who failed to respond to the group treatment was given a behavioural treatment based on feed-back of bladder pressure via an indwelling pressure-sensitive catheter and an auditory signal, the pitch of which was a function of bladder pressure. Follow up for 3 months was offered to all patients; the questionnaires were given again at 1 and 3 months after treatment.

Results

3 patients completed only the MHQ, which had to be filled in at the interview, whereas the other questionnaires could be returned by post. 2 patients were excluded from the present study because they suffered from nocturnal enuresis and were virtually symptom free during the day. This left 26 patients who completed all their questionnaires and on whom data analysis is based. The 26 patients were divided into two equal groups of 13 based on MHQ scores. Those with the highest MHQ scores were termed the most neurotic group, and those with the lowest MHQ scores, the least neurotic group. Table I shows the mean scores for the 2 groups, with the means for a normal population. The EPI yields two scores, Extroversion and Neuroticism.

Table I

Mean Questionnaire Scores

	Middlesex Hospital Questionnaire (MHQ)	Eysenck Personality Inventory (EPI)		Fear Survey Schedule (FSS)
		Neuroticism	Extraversion	
Most neurotic (13)	50·7	19·6	12·8	52·4
Least neurotic (13)	26·2	12·4	14·5	22·9
Normal population	27·6	12·7	13·0	25·3

Table II

Results of Treatment

	Refused treatment	Degree of improvement of symptoms			
		Great	Moderate	Slight	None
Most neurotic (13)	3	5	3	1	1
Least neurotic (13)	4	1	1	2	5

The difference between these two groups is reflected in the treatment outcome (Table II). In the most neurotic group 3 patients refused treatment: of those that accepted, 5 were considerably and 3 were moderately improved, 1 was slightly improved and 1 remained unchanged at the 3-month follow-up. The improvement coincided with a fall in the MHQ scores. In the least neurotic group, 4 patients refused treatment: of those who accepted, only 1 was considerably improved, 1 moderately and 2 slightly improved. 5 patients showed no improvement, of whom 2 ceased treatment prematurely. Mean MHQ scores had risen slightly at 3 months.

Discussion

These results (Table I) show that the most neurotic group score very highly on all 3 measures of neuroticism, whereas the least neurotic group actually scores below normal on all 3 measures, and is abnormally extroverted. There are 2 explanations for these findings. One is that the 2 groups really do differ as indicated by the scores with regard to neurotic symptoms and behaviour. The other is that those in the least neurotic group are denying or disclaiming neurotic symptoms. The authors favoured the latter explanation, for the following reasons.

The least neurotic group contained the patients who appeared most disturbed according to their biography and medical history. Their symptoms were often bizarre or atypical, with pain in areas other than the bladder as a common feature. The majority had grossly disturbed interpersonal relationships, had recently lost a close relative, or had a history of repeated bereavement. The husbands of 4 of these women had been involved in serious accidents at work or on the road. In each of these 4 women the urinary symptoms appeared related to their husband's accident and to the stress of coping with the consequent disablement and loss of earnings and status.

When offered psychological treatment for their urinary symptoms, several requested operations instead, and 1 felt that removal of her bladder was the only answer. Others shifted the focus to symptoms elsewhere. 3 were more concerned about the smell of leaked urine than the incontinence itself, but none of the authors ever noticed such a smell. Many had had repeated surgical interventions, not only of a gynaecological but also of a general surgical or orthopaedic nature; 6 patients had seen doctors in at least 4 different specialities within the past few years.

It was striking that those who accepted treatment all sat through from 4 to 10 hours of interviews and subsequent treatments, but *on no single occasion* did any patient leave the room prematurely on account of urgency. Only once did a woman leak any urine, and in such a small amount that it was noticed only as a spot of dampness on her chair at the end of a treatment session. This virtual dryness was in stark contrast with the complaints of some of these patients of almost constant leakage, and it helps explain why none of them wore protective undergarments.

As a group, these patients were initially very reluctant to accept that they had any emotional or interpersonal problems. They became defensive at the suggestion of seeing a psychiatrist, even if it was made tactfully. They focused all their dissatisfaction on to bodily complaints and symptoms, and tended to ignore or deny any possible relationship between these symptoms and their emotions. They were persistent in seeking a physical basis, such as bladder or kidney infection for their symptoms, even if it had been clearly demonstrated that this was not the case. They often sought further pharmacological or surgical intervention, even though in the past such treatment had invariably produced only temporary symptom relief, or a shift of symptoms to another area. Indeed, it seemed easier for several of these women to undergo repeated operations which failed, rather than examine the massive interpersonal and emotional problems which appeared to underly their symptoms. They could not do this without the collusion of a proportion of doctors. This collusion in denying a possible emotional or interpersonal basis for their symptoms was also evident in the less disturbed cases in the least neurotic group, and is illustrated by a case history.

Case History

A middle-aged patient had experienced frequency, with later development of a constant aching pain in the bladder, since her husband had had a severe coronary thrombosis. She had been treated several times for cystitis, in the absence of proven infection, and clung to this as an explanation for her symptoms. It became clear during the interview that, in spite of severe angina, her husband favoured regular sexual intercourse. Almost invariably, anginal pains forced him to cease prematurely, which both frightened and frustrated his wife. The couple were totally unable to discuss the problem, and the patient's way of dealing with it was to use her bladder symptoms as an excuse for avoiding intercourse. Predictably she dropped out of treatment very early, preferring to retain the symptoms, or at least the hospital visits which substantiated them, rather than tackle the underlying problem.

By contrast, the most neurotic group were much more willing than the least neurotic group to acknowledge and discuss underlying emotional and interpersonal problems, which were often of a temporary nature, or relatively mild. They infrequently showed the reported features of the least neurotic group, and their symptoms were much more typical of Frewen's description of urge incontinence. Frequency was a more prominent complaint in this group than in the least neurotic group, who tended to emphasise incontinence.

Our findings coincide very closely with those of Frewen (1972). We believe we can explain why some of his patients failed to respond to his treatment programme. They probably corresponded to those patients in our least neurotic group, with atypical symptoms and major underlying emotional and interpersonal problems. So great or insoluble are these problems that patients may prefer to deny them and to focus their dissatisfaction on physical symptoms. In this way they receive sufficient support, care and encouragement from doctors and other health workers to enable them to continue with their struggle through life. Inevitably they tend to resist symptomatic improvement, or find new symptoms, in order to maintain the status quo. They may also exaggerate symptoms, or emphasise symptoms which they have learnt will elicit the desired response from their doctors.

Although emotional and interpersonal problems appear intimately associated with urgency incontinence, over a third of patients (group 1), usually with atypical symptoms and severe underlying problems, appear relatively inaccessible to psychiatric help. A tactful invitation to see a psychiatrist may ease some of their difficulties. However, a greater awareness of the syndrome of a chronically complaining woman seeking fruitless intervention from a succession of specialists might be more helpful. About one-third of the patients (group 2), because of the complexity of underlying problems, would probably benefit from appropriate psychiatric intervention. The remainder (group 3) appear to require only a comparatively brief but firm and comprehensible exploration of the relationship between their life style and the emotions it generates, and their bladder activity. This does not necessarily require a psychiatrist. *In any event it is important to exclude organic bladder or urethral conditions before enlisting psychiatric assessment, because of the subsequent harmful effect which an incorrect psychiatric label might have on the patient's future medical career.*

Finally, we offer to the non-psychiatric clinician a tentative and broad guide to classification, based on (i) the patient's response to a question like "Do you think there may be an emotional or nervous element to your symptoms?" and (ii) EPI or MHQ scores. A hostile or overdefensive response to the question and low neuroticism or MHQ scores, indicate group 1. A constructive or positive response to the question and high neuroticism or MHQ scores, indicates group 2. An equivocal response to the question and neuroticism and MHQ scores close to normal, indicate group 3. In spite of the broad nature of this guide, and the likelihood of overlap between groups, we believe it will prove to be useful.

Summary

26 patients with frequency, urgency and urgency incontinence, without bladder or urethral abnormality, underwent psychiatric evaluation. They were divided into 2 groups according to the degree of neuroticism found.

Treatment by group and individual psychotherapy showed that approximately one-third of the patients benefited considerably, one-third refused treatment or ceased prematurely and one-third improved slightly or not at all.

The importance of excluding organic bladder or urethral disease prior to psychiatric assessment is stressed.

We should like to thank our colleagues for having referred the patients for assessment and the Departments of Radiology and Physics for their help with the urodynamic investigations. The work has been financially supported by St George's Hospital Medical School.

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The Authors

R. Julian Hafner, MD, MPhil, MRCPsych, Senior Lecturer, Department of Psychiatry.
Stuart L. Stanton, MRCOG, FRCS, FRCSE, Senior Lecturer and Honorary Consultant, Urodynamic Unit, Department of Obstetrics and Gynaecology.
John Guy, MB, BS, Registrar, Department of Psychiatry.

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Closed Catheter Drainage and Urinary Infection – a Comparison of Two Methods of Catheter Drainage

A. K. M. S. ISLAM and JOHN CHAPMAN
St Peter's Hospitals and Institute of Urology, London

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The use of a closed system of urinary catheter drainage with a plastic bag containing chlorhexidine has been advocated as a means of preventing postoperative urinary infection (Webb and Blandy, 1968; Symes *et al.*, 1972). In St Peter's Hospital in 1972 drainage systems using "single use" plastic bags and "continuous use" bags with chlorhexidine were tested in order to decide which would be the better for routine use. In addition an attempt was made to evaluate the influence that the type of operation, duration of catheter drainage and chemotherapy had on the incidence of infection.

Patients and Methods

2 groups of patients (aged between 17 and 85 years), who had been admitted to one ward and required continuous catheter drainage, were entered into the trial. Each group was studied over a 4-month period.

Group 1 (90 patients)

The catheter drained via a connecting tube into a sterile disposable plastic bag with a flutter valve at the input port to prevent retrograde flow. Full bags were replaced using standardised aseptic precautions.

Group 2 (110 patients)

The catheter was connected by a sterile tube to a drainable plastic bag with an outlet tap at the bottom through which 10 ml of 5% aqueous chlorhexidine solution had been introduced from a prepared sachet when the bag was empty. When the bag was full, urine was drained through the outlet tap and more chlorhexidine was added.

Table I

The incidence of postoperative urinary infection during catheter drainage (all cases with sterile preoperative urine)

	No. infected post-op./no. of cases		
	Group 1	Group 2	Totals
Overall incidence of infection	23/69 (33·3%)	24/79 (30·4%)	47/148 (31·8%)
All endoscopic procedures	15/45 (33·3%)	10/44 (22·7%)	25/89 (28·1%)
All open surgery	8/24 (33·3%)	14/35 (40·0%)	22/59 (37·3%)
TUR of prostate or bladder tumour	12/35 (34·3%)	7/30 (23·3%)	19/65 (29·2%)

Table II

Serological type and phage-typing pattern of *Ps. aeruginosa* from catheter urine of patients infected with similar strains. November 1972-June 1973

Case no	Chlorhexidine in bag	Serological type	Phage-typing pattern () = weak reaction	First isolation	Remarks
1	Yes	6	44, 68, 73, 109, 1214, M4, M6, Col. 11	11 Nov.	Unrelated strain
2-4	Yes	6	Similar phage-typing pattern*	26 Jan. and 01 Feb.	Infected pre-op.
5	Yes	6	(7), 21, (24), (F7), 119X, (M4)	02 Feb.	Bag urine contaminated with pseudomonas†
6	No	6	44, 68, (F8), 109, 119X, (124), (M4), 188 I	06 June	Unrelated strain
7	No	9	68	23 Feb.	Infected pre-op
8	No	9	68	05 Mar.	Bag urine contaminated with pseudomonas‡
9	Yes	5d	68, 119X	09 Feb.	Pseudomonas in catheter urine from 9-19 Feb.
10	Yes	5d	68, 119X	10 Feb.	Bag urine contaminated, catheter urine sterile
11	Yes	5d	68, 119X	17 Feb.	Could have acquired infection from case 9

* These strains did not differ more than 2 strong phage reactions.

† Drainage tube (bladder) urine yielded *Strep. faecalis*, but bag urine had *Ps. aeruginosa* in addition and its phage type was indistinguishable from case 3 strain.

‡ Drainage tube (bladder) urine yielded *Staph. epidermidis*, but bag urine had pseudomonas in addition.

Mid-stream specimens of urine (MSU) from all patients were examined bacteriologically on admission and 24 hours and 4 weeks after removal of the catheter and daily catheter specimens of urine (CSU) were taken by needle aspiration of the drainage tube. All samples were cultured quantitatively using a surface viable count method, and "significant bacteriuria" was diagnosed if the colony count was greater than 10^5/ml of urine. Organisms isolated were identified by standard methods and *Escherichia coli* and *Pseudomonas aeruginosa* species were serotyped.

Results

Table I shows the incidence of postoperative urinary infection in those patients whose pre-operative urine was sterile and it will be seen that 23 of the 69 patients in Group 1 (33·3%) and 24 of the 79 Group 2 cases (30·4%) developed a urinary infection during the period of catheter drainage. This difference is not statistically significant.

The type of operative procedure did not significantly alter the postoperative infection rate in either group (Table I) though it was noted that the highest incidence of infection occurred after urethroplasty (12 out of 24 patients infected). *The duration of catheter drainage* was, however, a significant factor; if maintained for more than 6 days over 50% of patients became infected, contrasting with a 9% infection rate when the catheter was *in situ* for no longer than 3 days. Similarly, infection occurred more frequently in patients whose catheter needed to be changed (9 of 17 becoming infected) or whose bladder was washed out with sterile saline (9 of 20 infected). When continuous bladder irrigation with sterile saline was maintained infection occurred less commonly in the Group 2 patients, only 1 of 7 of whom became infected. The use of antimicrobial agents did not significantly alter the incidence of infection.

Bacteriological Findings

The predominant organisms isolated from pre and postoperative urine were *E. coli*, *Ps. aeruginosa* and *Staph. epidermidis*. The last-named appeared to be a significant causal organism in postoperative infection (Fig. 2).

The serotype and phage-typing patterns of the pseudomonas isolates from CSU of patients with similar strains are shown in Table II. The clustering of similar pseudomonas serotypes suggests the possibility of cross-infection. However, most cases were infected before admission and appeared unrelated to others although there is perhaps the possibility that case 11 could have become infected from case 9. There were 3 instances of contamination of bag urine. The overall sensitivity of 128 isolates from CSU was as follows:

44% were sensitive to ampicillin, 63% to cephalothin, 64% to carbenicillin, 95% to gentamicin, 71% to colistin, 52% to tetracycline, 60% to cotrimoxazole, 52% to nitrofurantoin and 45% to nalidixic acid. 4 of the 34 pseudomonas strains were resistant to gentamicin and 13 to carbenicillin.

Response to Treatment

In all, 99 patients were found to have infected urine during this study—52 before operation and 47 in the postoperative period. Of the 64 patients who received antimicrobials the urine (MSU) became sterile after removal of the catheter in 28 but in the remaining 63 the infection persisted; in

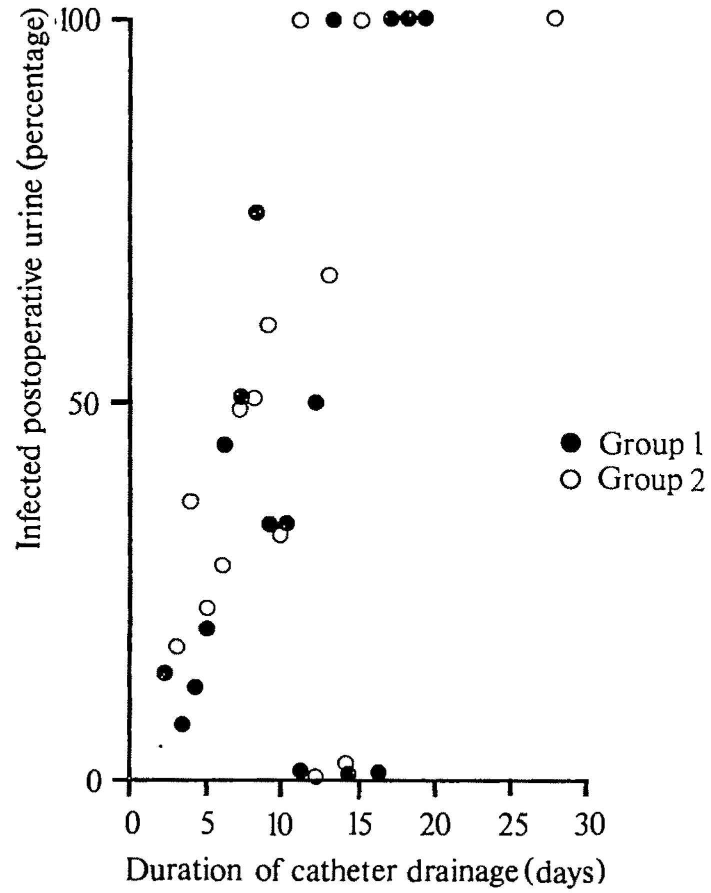

Fig. 1. The relationship between the incidence of postoperative urinary infection and the duration of catheter drainage in Groups 1 ($P < 0{\cdot}01$) and 2 ($P < 0{\cdot}001$) cases.

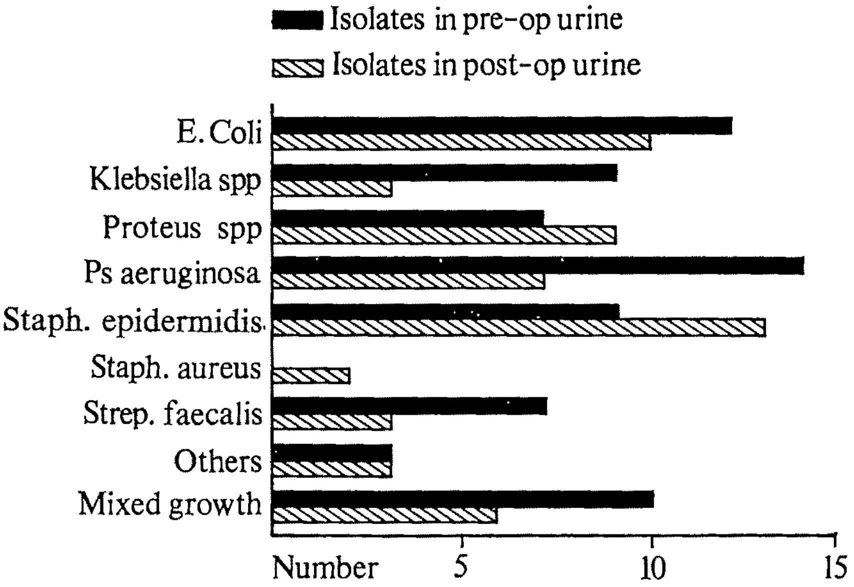

Fig. 2. The organisms isolated from infected pre and postoperative urine.

33 of these the organisms were resistant to the drugs given (usually ampicillin and penicillin administered prophylactically against pseudomonas, resistant *E. coli* or penicillinase-producing *Proteus mirabilis*). 33 of the 35 patients who did not have chemotherapy were still infected at follow-up. Only in 2 patients urine cleared spontaneously 4 weeks after removal of the catheter.

Discussion

This study failed to demonstrate that either of the 2 methods of bladder drainage tested was superior to the other in reducing the rate of postoperative urinary infection. Our current practice, since completing the investigation, is to employ a "continuous use" plastic bag with a flutter valve at the input port and an outlet tap at the bottom (*i.e.* as in Group 2 patients but without the addition of chlorhexidine). We also advocate replacing the bag with a fresh one when catheter drainage lasts for more than 3 days.

The reported incidence of urinary infection following transurethral resections varies considerably. Jackaman and Chisholm (1975) found bacteriuria in 18%, Shapiro, Santamarina and Harrison (1974) in 40%, and Brehmer and Madsen (1972) in 20% and, in our series, the rates were 34% for Group 1 and 23% for Group 2 patients. All these figures clearly indicate that urinary infection following urological operations requiring a period of catheter drainage is still unacceptably high, even in specialist units. Preoperative skin/meatal disinfection was not standardised in the present study, though 0·5% aqueous chlorhexidine solution was frequently used; in a few cases an intra-urethral disinfectant was instilled before instrumentation. The use of an alcoholic chlorhexidine to clean the meatal skin before operation and the universal use of an intra-urethral disinfectant (Webb and Blandy, 1968; Symes *et al.*, 1972). might have led to some reduction in the infection rate.

The urinary infection detected in 9% of our patients within the first 3 days of catheter drainage (Fig. 1) might well have been initiated by organisms carried into the bladder from the urethra during instrumentation, whereas infection arising later is more likely to be due to the bacteria colonising the urethra while the catheter is *in situ*. At this stage any manipulation, such as change of catheter of a bladder wash-out, would be likely to transfer a heavy inoculum of bacteria into the bladder, and the fact that these manoeuvres resulted in measurable infection in between 44% and 57% of the patients in the present series is good evidence that the urethra is indeed the source of infection. These findings therefore support the views of Kass and Schneiderman (1957), and Brehmer and Madsen (1972) who reported a close correlation between urethral and perineal colonisation and bladder infection during catheter drainage.

In a few of the cases in the present series urine samples were taken direct from the drainage bag. Some of these yielded a growth of bacteria different from those found in the drainage tube urine collected at the same time. This occurred more often with the Group 2 patients being managed with bags using chlorhexidine, which was therefore suspected as a source of contamination. But as samples of the chlorhexidine sachets were found to be sterile this was eliminated as a cause and it is concluded that the most likely explanation is that there was a breakage of the closed drainage system.

Routine chemoprophylaxis was not undertaken during this study, but 48 of the 148 cases with sterile preoperative urine had antimicrobials during catheter drainage and in another 10 cases these were prescribed after removal of the catheter. Ampicillin (33 cases) and penicillin (5 cases) were the agents mostly used but the infection rates between the treated and untreated were not significantly different. In retrospect it is felt that cotrimoxazole would probably have been a more appropriate drug as 60% of the isolates were sensitive to it.

During the course of this study 8 patients were suspected of having a bacteraemia and in 6 of them the urine was infected at the time. It is suggested that patients on catheter drainage should have their urine examined at about 3-day intervals and should be treated, on the basis of sensitivity tests, for any infection that is found. Treatment should not be withheld in the hope of spontaneous sterilisation of the urine after removal of the catheter, because our finding, contrary to the experience of others (Clarke and Joress, 1960; Jackaman and Chisholm, 1975), shows that in only 2 of the 35 cases with infected urine was there a spontaneous clearing of infection at follow-up without chemotherapy.

Summary

The incidence of urinary infection following urological operations is compared using 2 methods of closed catheter drainage in 214 patients.

No significant difference was observed. The overall infection rates for the whole series were 32%.

The most significant influence on the rate of infection appears to be the duration of catheter drainage.

Failure of chemotherapy to eradicate infection while the catheter was still *in situ* was mostly due to the use of inappropriate antimicrobials.

Only 2 of the 35 cases with infected urine had succeeded in clearing their infection at the 4-week follow-up without chemotherapy.

We wish to thank Dr R. C. B. Pugh and Prof. J. D. Williams (London Hospital Medical College) for their advice and the urologists for access to patients. We are grateful to Dr M. T. Parker, Central Public Health Laboratory, Colindale, for serotyping pseudomonas.

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The Authors

A. K. M. S. Islam, MRCPath, Dip Bact, Lecturer, Department of Pathology.
John Chapman, FRCS, Senior Registrar (now Consultant Surgeon and Urologist, Northampton General Hospital).

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Adjuvant Immunotherapy with B.C.G. in Carcinoma of the Prostate

M. R. G. ROBINSON, C. C. RIGBY, R. C. B. PUGH and D. C. DUMONDE

Department of Urology, Pontefract General Infirmary; Departments of Pathology, St Peter's Hospitals and the Institute of Urology, London; Division of Immunology, Kennedy Institute of Rheumatology, London

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During the past decade adjuvant immunotherapy with Bacille Calmette-Guerin (B.C.G.) has been used in the management of several different human cancers. Direct tumour-B.C.G. contact may be necessary for effective immunotherapy (Baldwin, 1974) and the prostate is a suitable organ for intratumour injection. In addition, immunotherapy is more likely to be effective if the bulk of the tumour has been destroyed or inactivated by conventional surgery or endocrine therapy.

We have already reported the chronic tuberculin-type hypersensitivity reactions produced by B.C.G. in the malignant prostate of 6 patients whose disease was no longer controlled by conventional treatment (Robinson *et al.*, 1976). This paper describes the clinical and histopathological findings when B.C.G. adjuvant immunotherapy was given to 8 previously untreated patients with advanced prostatic cancer shortly after conventional transurethral resection of the primary lesion and orchidectomy.

Patients and Method

The project was approved by the Ethical Committee of the Pontefract General Infirmary. The patients were all aware that they were participating in a Research Project and would receive a new experimental treatment by B.C.G. injections directly into the prostate gland.

Table I

Clinical Features. Patients having Adjuvant B.C.G. Immunotherapy after T.U.R. and Orchidectomy

Patient	Age	Stage	Mantoux	No. of B.C.G. injections	Pyrexia	Comment
R. S.	77	III	Positive	6	++	Haematemesis. Duodenal and oesophageal ulcers. Died 2 months after therapy (head injuries, recurrent haematemesis).
R. C.	65	III	Positive	6	+++	Rectal bleeding after 5th injection. Died 2 months after treatment (myocardial infarction).
J. A.	68	III	Negative	6	++++	Deep-vein thrombosis right leg after 6th injection. Died (massive intestinal haemorrhage after 1st dose Heparin and Warfarin).
A. C.	83	III	Positive	3	+++	Coagulation studies normal. Alive and well.
W. S.	65	III	Positive	3	+++	Coagulation studies normal. Alive and well.
F. D.	77	III	Positive	3	++++	Coagulation studies normal. Alive and well.
H. R.	68	IV	Positive	3	+++	Coagulation studies normal. Alive. Bone pain. Cytototoxic therapy with Mephalon.
H. W.	69	IV	Negative	3	++	Coagulation studies normal. Alive and well.

Table II

Prostate Histopathology

	Before B.C.G. injections				After B.C.G. injections						
Patient	Grade of adenocarcinoma	Cellular infiltrate*			Sequential specimen number	Cellular infiltrate*					Tumour cell necrosis
		L	PN	PL		L	PN	PL	M	MG	
R. S.	High	+	0	0	1	+	+++	0	+	0	0
					2	++	++	+	+	0	0
					3	+++	++	+	+++	++	0
					4	+++	++	+	+++	++	+
					PM	+++	++	+	+++	++	+
R. C.	Medium	+	0	+	1	++	+	+	0	0	0
					2	++	+	+	++	++	+
					3	++	+	+	++	++	+
					PM	+++	++	++	+++	+	+
J. A.	Low	+	0	0	1	+	0	+	0	0	0
					2	+	0	0	0	0	0
					3	+	+	+	0	0	0
					PM	++	0	+	+	+	+
A. C.	High	+	0	+	1	+	+	0	0	0	0
					2	++	+	+	++	+	+
					3	++	+	+	++	+	+
W. S.	Medium	0	0	0	1	0	0	0	0	0	0
					2	++	+++	+	++	+	0
F. D.	Medium	+++	+	+++	1	+	+	0	0	0	0
					2	+	0	+	0	0	0
					3	++	0	++	0	0	0
H. R.	Medium	0	0	0	1	++	0	+	+	+	0
					2	++	0	+	++	+	+
					3	+	0	+	+	+	0
H. W.	Medium	0	0	0	1	0	0	0	0	0	0
					2	+	0	0	0	0	0
					3	+	0	0	0	0	0

* L = Lymphocytes; PN = Polymorphonuclear leucocytes; PL = Plasma cells; M = Macrophage; MG = Macrophage granulomata.

5 patients had extension of the disease beyond the prostatic capsule (Stage III disease) and 3 had skeletal metastases (Stage IV) (Table I). Before treatment they were Mantoux tested. The bulk of their primary tumour was removed by transurethral resection and the activity of residual tumour suppressed by bilateral total orchidectomy.

Before and during adjuvant immunotherapy prostates were biopsied for histological studies using a transrectal Tru-cut needle. Glaxo freeze-dried vaccine was injected into tumours, transrectally, through multiple puncture sites in order to infiltrate the lesion widely. 1 ml was given at the first injection and the amount increased by 1 ml each week. 3 patients had 6-weekly injections and 5 had 3 weekly injections. Coagulation studies (bleeding time, prothrombin time, partial thromboplastin time, plasma fibrinogen) were performed before and during treatment in 5 patients.

Results

Clinical Features (Table I)

6 patients were Mantoux-positive and 2 Mantoux-negative before treatment. All the patients had a marked pyrexia for 48 hours after injection. Blood cultures were negative for organisms which

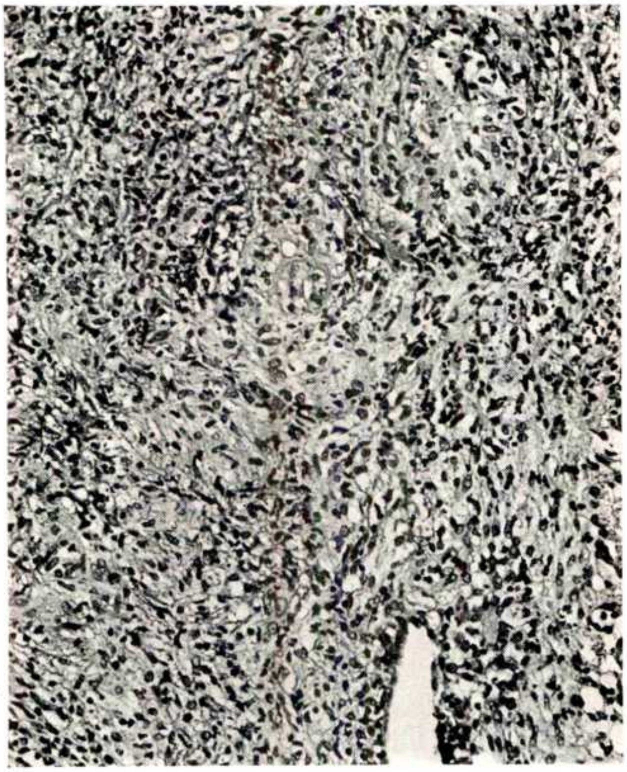

Fig. 1. Patient R. S. Prostatic biopsy after the 3rd B.C.G. injection. A large macrophage granuloma is present. H.E. × 40; Enlarged × 4.

might have contaminated the transrectal injection. This reaction was more marked in the Mantoux-positive patients than in our previously reported 6 patients. There was no clinical evidence of injury to the urinary tract. 3 patients, all of whom had 6 injections, had gastrointestinal haemorrhage during treatment. This occurred in one patient (J. A.) 24 hours after one dose of heparin and warfarin for a deep-vein thrombosis. He died 24 hours later and at post-mortem there was no evidence of a pulmonary embolus. A second patient (R. C.) had severe rectal bleeding after the 5th injection. He recovered initially but died of myocardial infarction 2 months after adjuvant immunotherapy with B.C.G. The third patient (R. S.), a known case of chronic peptic ulceration, had severe haematemesis after the 6th injection. At endoscopy he had multiple oesophageal and duodenal ulcers which appeared to be superficial and a biopsy of an oesophageal ulcer showed granulation tissue with lymphocytes and plasma cells. He died 2 months later following a head injury.

The 5 patients who had only 3 injections remain alive at intervals of 6 months to 1 year after treatment. They all had normal coagulation studies before and after treatment. 4 of these 5 have no symptoms and the 5th (H. R.) has metastatic bone pain.

Histopathological Examination

Following 1 or more B.C.G. injections prostatic biopsies from most of the patients indicated a delayed hypersensitivity reaction (Fig. 1). Cellular infiltration in diagnostic biopsies before B.C.G.

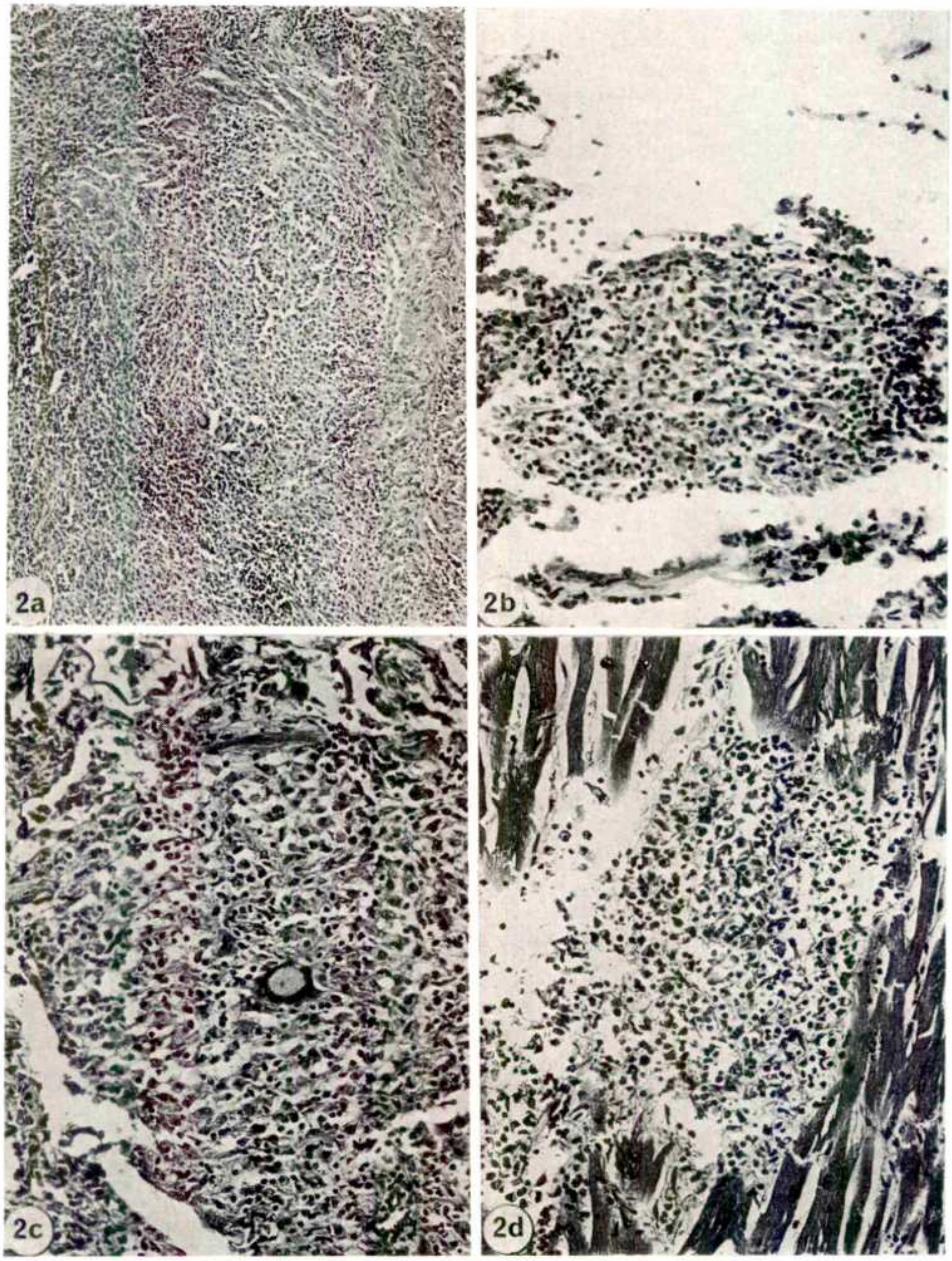

Fig. 2. Patient R. S. Granulomatous reactions found post mortem. *a*, Prostate; H.E. × 16; Enlarged × 4. *b*, Lung; H.E. × 40; Enlarged × 4. *c*, Heart; H.E. × 40; Enlarged × 4.

therapy was slight; but after B.C.G. injections lymphocytes and macrophages were present and often numerous, forming granulomatous lesions together with giant cells of a tuberculous type. Two patients, J. A. and H. W., were Mantoux-negative before treatment and systemic reactions to B.C.G. were less marked in both, although autopsy on one (J. A.) revealed a prostatic reaction, including some destruction of tumour cells. Where granulomatous lesions occurred in carcinomatous areas tumour cells were degenerate; but a hypersensitivity reaction was sometimes apparent in non-tumourous areas, and here the normal tissue was disorganised. Autopsies were performed on 3 patients (J. A., R. C. and R. S.); the prostate of each contained areas of macrophage infiltration and necrosis (Fig 2a) and in all three these lesions extended to the sub-rectal tissues. There was evidence of dissemination of the bacillus; scattered small granulomas were found in the lungs, liver and spleen in 3 patients and also in the myocardium of one of them (R. S.) (Fig. 2b, 2c and 2d). These 3 patients all had haemorrhagic episodes following B.C.G. injections but no vascular abnormalities were detected. The oesophageal ulcer and duodenal mucosa in patient (R. S.) showed a chronic inflammatory cell reaction, non-specific in nature.

Discussion and Conclusions

These results confirm the previous findings (Robinson *et al.*, 1976) that intratumour injections of B.C.G. produce tuberculin-type hypersensitivity reactions in human malignant prostates. On biopsy material this may be associated with degeneration of tumour cells, and at post-mortem large areas of necrosis have been associated with a granulomatous reaction.

The patients in this series developed a pyrexial reaction to B.C.G. immunotherapy which has been more marked than was found in our previous series of patients who had terminal disease. Also, as in the earlier account, there is no evidence that the therapy has injured the urethra, bladder or rectum.

The granulomas found at post-mortem in the lungs and liver are similar to those described by Sparks *et al.* (1973). The granulomatous lesion in the heart in patient R. S., perhaps surprisingly, did not cause clinical symptoms. In none of our patients was there clinical or biochemical evidence of hepatic dysfunction.

The most disturbing feature of the early part of this study was the gastrointestinal bleeding, which occurred after the 5th or 6th B.C.G. injection in no less than 3 patients. In 1, who died after minimal anticoagulant therapy, haemorrhage appeared to have been a contributory cause of death. In another, who had previously been known to have had a duodenal ulcer, bleeding occurred from granulomatous ulcers in the oesophagus and duodenum; this may have been related to the B.C.G. therapy. Accordingly, the B.C.G. course was shortened and the remaining 5 patients were carefully monitored haematologically. They were given only 3 injections; coagulation tests were normal both before and during treatment, and in no case did gastrointestinal bleeding occur.

Assessment of the significance of these results is difficult. There is no doubt that B.C.G. injections produced granulomatous lesions within the prostate itself and that in 5 cases there appeared to be obvious destruction of tumour cells due, in all probability, to the local presence of granulomas. But attempts to increase tumour damage by increasing the doses of B.C.G. led to the unexpected development of gastrointestinal haemorrhage. This occurrence, together with the additional finding of granulomatous dissemination beyond the prostate, discouraged the use of more than 3 doses of B.C.G. It is interesting that Whittaker *et al.* (1976), using the intravenous route in 11 patients with acute myeloblastic leukaemia, found widespread granuloma formation in 9 patients. Although no ill-effects could be attributed to the presence of these granulomas, they also considered that the potential dangers of B.C.G. immunotherapy required further investigation.

Further clinical studies to determine the dose, time interval between injections and the effect of B.C.G. adjuvant immunotherapy on prognosis are required in this disease.

Summary

8 previously untreated patients with Stage III and Stage IV prostatic cancer who had had the bulk of their primary tumour removed by transurethral resection, and residual tumour suppressed by bilateral total orchidectomy, were given adjuvant immunotherapy by direct injection of B.C.G. into the prostate.

The pyrexial reaction to, and the histological changes from B.C.G. have been more marked in the patients whose disease is no longer controlled by conventional therapy.

Granulomas have been found in the lungs, liver, myocardium, spleen and bone marrow. Granulomas in carcinomatous areas have been associated with tumour cell degeneration.

We wish to thank the Pathology Department at Pontefract General Infirmary for preparing the biopsy and post-mortem specimens.

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The Authors

M. R. G. Robinson, FRCS, FRCSE, Consultant Urologist, Pontefract General Infirmary, Pontefract.
C. C. Rigby, FRCPath., Department of Pathology, St Paul's Hospital, Lecturer, Institute of Urology.
R. C. B. Pugh, MD, FRCPath, Director, Department of Pathology, St Peter's Hospital.
D. C. Dumonde, FRCPath, Head of Division of Immunology, Kennedy Institute of Rheumatology.

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Sex Hormone Binding Globulin in Carcinoma of the Prostate

A. L. HOUGHTON, R. TURNER and E. H. COOPER

Department of Experimental Pathology and Cancer Research, University of Leeds

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The main sex hormones testosterone and oestradiol are bound in the serum to two types of protein:

(*a*) Albumin with low affinity but high capacity due to its high concentration.

(*b*) Sex Hormone Binding Globulin (SHBG), a β globulin with high affinity. This is a glycoprotein synthesised in the liver, with a molecular weight estimated to be 115000 (Rosner, Christy and Kelly, 1969).

The normal values of SHBG vary with age and sex, may alter in certain disease states and are influenced by administration of androgens and oestrogens. Vermeulen, Rubens and Verdonck (1972) found the mean values in normal adult men to be $5{\cdot}2 \times 10^{-8}$ M rising to $8{\cdot}2 \times 10^{-8}$ M over the age of 70. Anderson (1974) gives a mean value of $3{\cdot}2 \times 10^{-8}$ M in men (95% confidence limits, 1·85-5·53) and found the values to be a little over double in adult females; $6{\cdot}92 \times 10^{-8}$ M (95% confidence limits 4·22-11·3). In pregnancy the value may rise 5-10 times the normal adult female value (Anderson, 1974). In both sexes these values may be doubled in untreated thyrotoxicosis (Rosner, 1972). The value of SHBG in women on oestrogen contraceptive pills is significantly raised (Vermeulen *et al.*, 1969).

In a small number of men with carcinoma of the prostate treated with diethylstilboestrol (5 mg/day), Vermeulen found that the level of SHBG rose rapidly; values found were of the order of $20\text{-}30 \times 10^{-8}$ M within 2 weeks of the onset of treatment (Vermeulen *et al.*, 1969). Similarly Pearlman, Crépy and Murphy (1967) in 4 patients on oestrogen found considerable elevation of SHBG. By contrast the administration of androgens to female patients has been observed to cause a fall in SHBG (Vermeulen *et al.*, 1969).

We were interested to see what values of SHBG were obtained in a large number of patients with carcinoma of the prostate, particularly those treated by stilboestrol in doses of 1 mg or 3 mg daily. Many of these patients had received oestrogen therapy for some years; so we were able to see if SHBG levels remained high after as much as 7 years' treatment.

In recent years measurement of the total plasma testosterone by radioimmunoassay has been advocated to assess the androgen suppression caused by oestrogen administration in men with carcinoma of the prostate (Robinson and Thomas, 1971; Shearer *et al.*, 1973). The measurement of free testosterone has received little attention, being a more involved procedure. As there is an inverse relationship between SHBG and free testosterone in several conditions (Vermeulen *et al.*, 1972; Anderson, 1974; Stearns *et al.*, 1974), we have investigated whether the simultaneous measurement of total testosterone and SHBG could yield more information for the biochemical monitoring of cancer of the prostate than either alone.

Patients: 130 men with carcinoma of the prostate (Ca P) with various stages and treatments were studied. In some of them up to 4 measurements over a 9-month period were made. At the same time the patients were evaluated clinically and staged (TNM). This included subjective and objective assessment; full blood count, sedimentation rate, serum phosphatases, urea and creatinine. The patients had a skeletal survey either by conventional radiography or scintigraphy, according to the EORTC[1] protocol 30740.

In addition 27 elderly patients with benign prostate hypertrophy (BPH) were studied to provide controls of comparable age to men with carcinoma of the prostate. The assay was tested biologically by an examination of sera of 20 women in the third trimester of pregnancy.

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[1] European Organisation for Research on Treatment of Cancer.

Table I

Analysis of Variance and 95% Confidence Limits of the Means

	Group 1 BPH	Group 2 Ca Prost. No treatment	Group 3 Ca Prost. Orchidectomy	Group 4 Ca Prost. Stilboestrol 1 mg daily	Group 5 Ca Prost. Stilboestrol 3 mg daily	Group 6 Pregnant women
Number of patients	27	47	13	25	45	20
Number of samples	27	54	17	41	69	20
Mean SHBG* $\times 10^{-8}$ M	5·1±1·8	5·3±2·6	6·4±3·3	25·4±6·8	28·3±9·2	32·7±5·6
95% confidence	2·2–7·9	3·3–7·3	8·8–10·0	23·1–27·7	26·2–29·8	29·4–36·1

* ± S.D. Analysis of variance $F = 139$ ($t = 1{\cdot}96$ for $p = 0{\cdot}05$).

Methods

Venepuncture was performed between 0900 and 1200 hours. After separation the sera were stored at −20°C.

Testosterone was measured by radioimmunoassay using an antiserum with cross-reactivity of 40% with dihydrotestosterone (DHT). Since circulating DHT levels are about one-tenth of those of testosterone (Ito and Horton, 1970), results were not corrected for any DHT present.

About a quarter of the patients did not have any measurement of testosterone.

Gamma Glutamyl Transpeptidase (GGT) was measured by the enzymatic hydrolysis of the substrate L-glutamyl p nitroanilide using an automated technique (Haesen, Berends and Zondag, 1972). The enzyme is used as a sensitive marker of liver cell damage due to neoplastic infiltration.

Sex Hormone Binding Globulin (SHBG) was measured by a modification of Rosner's method (Rosner, 1972; Anderson, personal communication). In this modification in order to ensure saturation of binding sites, 4 concentrations of tritiated dihydrotestosterone (^{3}H-DHT) are incubated with aliquots of diluted serum.

The blank value for the radioactivity not bound to SHBG is provided by parallel serum samples with their SHBG saturated with excess cold DHT. The SHBG is precipitated with ammonium sulphate and the amount of ^{3}H-DHT precipitated as indicated by a fall in radioactivity gives a measure of SHBG binding site concentration.

Duplicate counts within the assay were accurate to less than 10%. Correlation between repeat assays on the same sample on different days was satisfactory ($r = 0{\cdot}74$).

We have arbitrarily classified the following levels of SHBG:

1. Normal (low) values	$<10\times10^{-8}$ M
2. Intermediate	$10-20\times10^{-8}$ M
3. High (pregnancy range)	$>20\times10^{-8}$ M.

Statistical Analysis

The results were compared by analysis of variance and calculation of the 95% confidence limits of the group means as described by Woolf (1968). The calculation was made using a Hewlett Packard Model 10 calculator.

Results

The composition of the population of samples assayed, the group means and 95% confidence limits of these means is shown in Table I. The values for BPH are comparable to those in normal and elderly men reported by Anderson (1974) and Vermeulen *et al.* (1972), falling between their mean values. The analysis of variance indicated highly significant differences are present among the group means

$$F\begin{bmatrix}5\\223\end{bmatrix} = 139\ (P = 0{\cdot}01).$$

Inspection of the 95% confidence limits of the means shows it is the patients with prostate carcinoma treated with oestrogen and the pregnant women who have higher SHBG levels than patients of all groups not receiving oestrogens. Further analysis for differences within these two major composite groups indicated there were no significant differences between groups not receiving oestrogens

$$F\begin{bmatrix}2\\95\end{bmatrix} = 1{\cdot}72\ (P = 0{\cdot}01).$$

A comparison of patients treated with oestrogens and pregnant women showed a significant difference in the group means

$$F\begin{bmatrix}2\\127\end{bmatrix} = 5{\cdot}63\ (P = 0{\cdot}01)$$

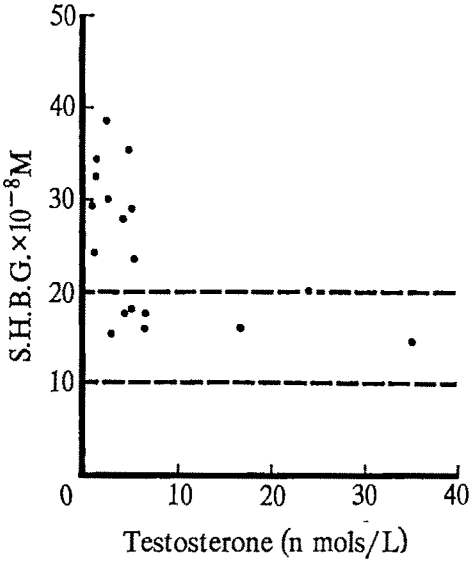
this was due to the difference between the pregnancy and 1 mg stilboestrol group ($t = 4{\cdot}4$ for 59 degrees of freedom).

The 2 results in the 3 mg stilboestrol group which lie in the normal range are from 1 patient who was severely incapacitated by widespread metastatic disease. After a short period on L phenylalanine mustard—when his SHBG level rose to 30×10^{-8} M—he died.

The results indicate that almost all patients on oestrogen, even in the low doses given here, show elevations of SHBG levels above the normal, those in the 3 mg stilboestrol group being slightly but not significantly greater than the 1 mg stilboestrol group. This accords with the observations of Shearer *et al.* (1973) on testosterone levels in patients on the same 2-dose regimes of stilboestrol, in which the fall in testosterone levels in these 2 groups was not significantly different.

Relationship between SHBG and Testosterone (Figs. 1 and 2)

In patients on 1 or 3 mg stilboestrol a day very low levels of testosterone can be associated either with intermediate or high levels of SHBG. The 3 values of testosterone lying within the normal range (8-27 nmols/l) belong to 2 patients, both on 1 mg stilboestrol daily. Possible explanations



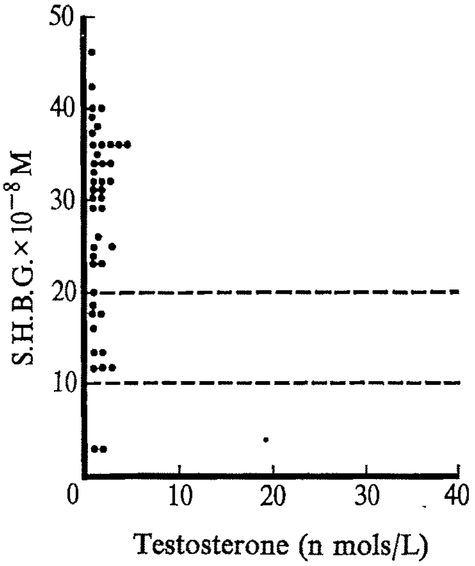


Fig. 1. SHBG and testosterone levels in patients receiving 1 mg stilboestrol per day. Horizontal dotted lines define the 3 arbitrary levels.

Fig. 2. SHBG and testosterone levels in patients receiving 3 mg stilboestrol per day. Horizontal dotted lines define the 3 arbitrary levels.

for this are that the patients were not taking the medication, or that it represents failure of suppression throughout the 24-hour period as noted by Shearer *et al.* (1973). 1 of them has since improved since orchidectomy.

Relationship between SHBG and GGT Levels

No correlation was found between serum SHBG and GGT levels indicating that a failure to induce high levels of SHBG was not due to hepatic cell damage.

Relationship between SHBG and Duration of Treatment

High SHBG levels were found in patients who had received oestrogens for up to 7 years. Very few measurements were made on patients who had been on treatment for less than 3 months, but high levels were often reached at 3 months. The patients who had been on treatment for more than 3 years had a higher mean SHBG than those treated for less than 3 years. Indeed, all patients in this group had values in the high range. One interpretation is that the level of SHBG increases with the duration of treatment. Another interpretation of this is that only those who reach high levels are likely to survive longer than 3 years. However, when the hypothesis was tested statistically with a chi-square test the difference between the expected and observed distribution were found to be not statistically significant.

Consecutive Measurements of SHBG (Table II)

16 patients had 3 consecutive measurements of SHBG at intervals of 2 to 3 months. The patient whose SHBG rose from a mean of 3 to 30 on L phenylalanine mustard is excluded. It can be seen that the levels did not vary greatly in the majority of patients.

Discussion

Current theories of the mode of sex hormone transport and uptake by prostatic epithelial cells and subsequent influence on RNA and protein synthesis suggest a complex mechanism involving a transport protein in the serum (SHBG) and receptor proteins for free hormones situated in the cytoplasm and nucleus (Liao and Fang, 1969).

Table II

Values of Consecutive SHBG Estimations at 2 to 3 Month Intervals

Patient	Stage (TM)	Daily dose stilboestrol	SHGB (1)	(2)	(3)
1	T_3M+	3 mg	35·9	29·4	36·2
2	T_3M+	3 mg	12·0	11·7	14·9
3	T_2M+	3 mg	23·2	17·5	13·8
4	T_1Mo	1 mg	20·0	23·2	19·8
5	T_3Mo	3 mg	31·4	17·8	32·3
6	T_3Mo	1 mg	16·0	15·8	14·4
7	T_1M+	3 mg	28·6	32·1	23·1
8	T_2Mo	3 mg	34·7	30·5	24·7
9	T_3M+	1 mg	17·9	29·3	20·2
10	T_3Mo	3 mg	23·5	31·4	28·8
11	T_1Mo	3 mg	34·8	31·2	33·5
12	T_3Mo	1 mg	17·7	15·6	29·9
13	T_0M+	3 mg	36·0	33·0	34·0
14	T_2Mo	3 mg	24·6	23·8	18·6
15	T_3M+	3 mg	39·8	31·8	25·3
16	T_2Mo	3 mg	34·2	38·0	26·0

In man, the levels of total testosterone and the unbound fraction fall with age, while the levels of SHBG rise (Vermeulen *et al.*, 1972). The unbound fraction is believed to constitute 1-3% of the total (Burke and Anderson, 1972) and is regarded by many as the metabolically active fraction (Lasnitzki and Franklin, 1972). Burke and Anderson (1972) have found that the unbound fraction is influenced by SHBG in such a way that high SHBG lowers the unbound fraction of testosterone while raising the unbound oestradiol. They have suggested that the oestrogen-induced rise of SHBG acts as a biological amplifier for oestradiol action, by preferential reduction of the unbound testosterone fraction (Burke and Anderson, 1972).

If testosterone by its metabolism is concerned with the continued growth of carcinoma of the prostate then any mechanism which reduces this growth is of theoretical importance at least. However, it is not certain whether the doses of oestrogens currently used yield sufficient tissue levels to influence metabolism directly (Jenkins and McCaffery, 1974).

SHBG is one of several proteins whose rate of synthesis is profoundly influenced by oestrogens. This topic has been reviewed in depth by Anderson (1974). Other proteins which are affected by oestrogens are corticosteroid binding globulin (Seal and Doe, 1962) and a number of acute phase reactant proteins, notably caeruloplasmin, which is raised, and others which may be depressed.

Some patients with carcinoma of the prostate treated with stilboestrol show an acceptable level of depression of total testosterone levels but fail to show a full scale rise in SHBG (i.e., fail to achieve the high SHBG levels found in pregnancy). From previous work on the relationship between unbound testosterone and SHBG (Burke and Anderson, 1972) it is possible that the patients with only a slight rise in SHBG induced by oestrogens have a higher level of biologically active unbound testosterone.

It is evident that, in the present series, abnormalities of the hepatic cells either resulting from direct invasion of the liver by prostatic cancer, a rare terminal event, or secondary effects from circulating tumour products could not account for these intermediate or low SHBG levels. The GGT levels with 2 exceptions were normal or slightly raised, and none of the values would suggest that the protein synthesis capacity of the liver was impaired. It is not known what controls the rise in SHBG during treatment with oestrogens.

It was thought that patients who had only low or intermediate levels of SHBG on oestrogen treatment might prove to respond less well clinically than those with a high rise. There were 16 patients who had shown intermediate or low value of serum SHBG. Of these, 8 were well without demonstrable metastases and of the others, 4 were certainly suffering severely from their disease. By the same clinical criteria only 4 of 54 patients with high values of SHBG were suffering severely; and while there seems to be a disproportionate number of very ill patients in the group with intermediate or low SHBG levels a chi-square analysis showed that this was not more than could be attributed to chance.

As a corollary we examined the SHBG levels of the 8 patients severely incapacitated by their disease—that is patients with low performance status, pain, multiple metastases and usually severe anaemia. The mean of 16 values was $22{\cdot}5 \times 10^{-8}$ M, lower than that of 94 observations in the fitter patients ($28{\cdot}3 \times 10^{-8}$ M). Analysis of variance showed this to be significant

$$F\begin{bmatrix} 1 \\ 108 \end{bmatrix} = 7{\cdot}88 \ (p = 0{\cdot}01)$$

and this was confirmed by an unpaired *t* test ($t = 2{\cdot}83$ for 108 degrees of freedom). Because of the nature of this disease the proportion of such clinically ill patients at any one time is likely to be small and caution should be exercised in drawing conclusions based on comparisons of results in unequal groups. Nevertheless there are indicators that patients on oestrogens who have values of SHBG which are below the high range may be at a disadvantage. Further data could establish this hypothesis.

Summary

Sex Hormone Binding Globulin (SHBG) was measured in 130 patients with carcinoma of the prostate.

Its level is raised in patients treated with oestrogen and it is possible that this may be of prognostic significance.

The possible relevance of SHBG in oestrogen-treated patients is discussed.

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The Authors

A. L. Houghton, FRCS, Urological Research Fellow.
R. Turner, M.Phil, LRIC, Analyst.
E. H. Cooper, MD, DSc, FRCP, Professor.

ABSTRACTS OF THE PROCEEDINGS OF THE UROLOGICAL SOCIETY OF AUSTRALASIA

29th ANNUAL GENERAL MEETING, HONG KONG, 1976

President:	I. F. Potts (Sydney)
Honorary Secretay:	H. M. Learoyd (Sydney)
Editor:	J. P. Maddern (Adelaide)

Emergency Cystectomy: Indications and Results

By C. H. Leong, MBBS(HK), FRCS, FRCSE, FACS

Henry H. Y. Yu, MBBS, FRACS
Queen Mary Hospital, Hong Kong

The advent of modern anaesthesia has reduced the mortality of total cystectomy which is now a recognised form of treatment for invasive bladder cancer in the well-prepared patient. There are occasions however, when such a procedure may need to be performed as an emergency.

In the 5-year period from 1969 to 1975, a total of 55 total cystectomies were done in the University Department of Surgery, Genito-urinary Service. Of these, 9 cases (16·4%) were done as an emergency. 5 patients required an emergency cystectomy for uncontrollable bleeding and repeated clot retention despite massive blood transfusions and continuous bladder irrigation. 4 of these patients bled actively from their tumours and 1 patient from irradiation cystitis. 2 patients had an iatrogenic intraperitoneal bladder perforation. Attempts to repair the rupture were considered unwise as the perforation went through the tumour. 2 patients had an incorrect preoperative diagnosis. Both were thought to have a benign hypertrophy of the prostate. 1 was found to have a fungating carcinoma of the prostate, the other was found to have a bladder tumour infiltrating the prostate.

In 5 patients the cystectomy was performed with a pelvic block dissection while in the other 4 cases a simple total cystectomy was done. All had urinary diversion using an ileal conduit.

All 9 patients stood operation well. 1 patient, who had a ruptured carcinoma of the bladder, died 20 days after the procedure, apparently from septicaemia. 4 patients died at periods of from 3 to 20 months from tumour secondaries. All were highly malignant tumours. One patient died after 20 months from a persistent intestinal fistula following secondary exploration for intestinal obstruction.

3 patients are well after periods ranging from 18 months to over 2 years. 2 of these had bladder cancer which was followed by postoperative irradiation. The third patient had a malignancy of the prostate and was treated subsequently by bilateral orchidectomy and oestrogens.

Endoscopic Incision of the Bladder Neck

By Robert D. Wines, MB. BS. (SYD), FRCS(ED), FRCS(ENG), FRACS
Royal Prince Alfred Hospital, Sydney

The contribution to outflow obstruction and the production of symptoms by the smooth muscle of the bladder neck and prostatic capsule is often ignored, prominence being given to the prostatic adenoma. Opinions differ as to whether a true bladder neck sphincter exists, but recent work has shown the effects of the andrenergic nervous system on urethral muscle, explaining how bladder distention, temperature, psychological state, intercourse, and sympathomimetic drugs affect urethral closural pressures. Now neurogenic bladder instability has been shown in males to occur in response to outflow obstruction and may account for some presenting symptoms, and others that may persist following prostatectomy.

Transurethral incision of the bladder neck was performed using a technique similar to that of Orandi, but incisions were made deeper into the capsule and bladder neck, and stopped at the proximal part of the veru to avoid damage to ejaculatory ducts.

The procedure was performed on 57 patients (54 males, 3 females) (Group A: 33 normal patients, Group B, patients suffering from a psychiatric disorder) presenting with retention or with symptoms of prostatism. Most patients postoperatively experienced symptomatic improvement in urinary stream (Group A: 25 of 29), often equal to that as if a transurethral resection had been performed. Most striking improvement, however, was in irritative symptoms such as nocturia and urgency, possibly due to a reduction in bladder instability. For the same reason, marked improvement in the urinary control was observed in the psychiatric group postoperatively simplifying their nursing care.

Best results were obtained in younger men with small prostates who had given a "non-competitive stream" history preoperatively. All patients having sexual intercourse ejaculated postoperatively. Three patients required prostatectomy.

Long Term Complications of Enterocystoplasty

By WILLIAM K. KERR, MD
Toronto Hospital for Tuberculosis, Ontario, Canada

The use of segments of bowel: ileum, colon or caecum to enlarge the bladder or replace it in continuity with the urethra was applied in 72 cases during the past 20 years.

29 cases had an enterocystoplasty performed after subtotal cystectomy for benign bladder lesions where the prostate and bladder neck were preserved as well as the external sphincter. 18 operations were for tuberculous contracture, 7 for Hunner's Ulcer and 4 for neurogenic bladder. Of these cases, 25 have been followed from 5 to 20 years. Only 1 death has resulted. However, some progressive deterioration in renal function has been noted due to retention and hydronephrosis in about 50% of these cases, despite bladder-neck resections and triple voiding. Some cases have required cutaneous diversion. All the patients in this group, however, were continent.

In the second group, enterocystoplasty was performed after total cystoprostatectomy for carcinoma of the urinary bladder in which the bowel was anastomosed to the membranous urethra, thus depending entirely on the external sphincter to provide urinary continence. There were 43 such cases, 39 males and 4 females. In 2 of the males, a cystectomy was subtotal, 1 because the bladder was thought to have interstitial cystitis and the other because previous radiotherapy had created adhesions which necessitated the prostatic capsule and seminal vesicles being retained. Both developed local recurrence. Of the 4 females, 1 died postoperatively, 2 were diverted for incontinence, leaving 1 female patient for long-term review who still has her urethra intact. In this group of patients the main complication is incontinence. The renal status has with few exceptions remained remarkably stable. At least 80% of these cases have had a satisfactory renal function in follow-up periods as long as 15 years. Incontinence has been present in over 50%. It has been noted that once incontinence has been evident for 6 months there is little or no subsequent improvement. No calculi have been recorded in these 72 cases, it is thought that the use of catgut has been a factor in this. Mucus continues to be secreted with little change even after many years. Urethral recurrence of cancer has occurred in 2 patients out of the 43.

From the point of view of complications, there has been little difference whether ileum, sigmoid colon or caecum has been used. The ileum, however, seems the most satisfactory segment of bowel to use as it is cleaner, more mobile and lends itself to conversion to a cutaneous stoma in the event of failure.

Enterocystoplasty has the disadvantages of incontinence in patients with hydronephrosis in the benign cases which must be balanced with the rehabilitation achieved and the patient's age, prognosis, socio-economic and geographic status. Long-term follow-up is required in all.

Augmentation Cystoplasty in Small Contracted Bladder

By C. H. LEONG, MBBS(HK), FRCS, FRCSE, FACS
G. B. ONG, OBE, MD, FRCS, FRCSE, FACS, FRACS
Queen Mary Hospital, Hong Kong

Tuberculosis of the genito-urinary tract is still endemic in Hong Kong. Furthermore it commonly affects the prime of life. When the pathology involves the bladder the resultant lesion is that of a small contracted bladder. These patients are rendered socially unacceptable and in later stages progress into terminal renal failure as a result of severe bilateral ureteric reflux, unless a bladder enlargement is performed at an early stage.

A total of 14 patients with tuberculous contracted bladder have been seen in the genito-urinary service of the Department of Surgery, University of Hong Kong, since 1958. These bladders had a volume ranging from 15 to 75 ml. Augmentation cystoplasties have been performed on them using different parts of the gastrointestinal tract. 4 patients had a colocystoplasty using sigmoid colon, 3 patients had ileocystoplasty as a two-stage procedure. The first stage is the construction of a Bricker's cutaneous uretero-ileostomy while the second stage is to patch the ileal loop on to the bladder remnant. 6 patients had gastro-cystoplasty using the pyloric antrum of the stomach to enlarge the bladder. 1 patient had an ileo-caecal cystoplasty.

Our results show that all 4 organs are capable of producing a good reservoir effect and contract satisfactorily to completely expel the urine. Except for the pyloric antrum, the other 3 hollow organs used for bladder enlargement have the common disadvantage of absorption of chloride, excessive production of mucus, and alkalinisation of urine. The pyloric antrum on the other hand excretes chloride, acidifies urine and thus prevents the formation of staghorn calculi in the kidney and minimizes the chances of positive urinary culture. A total of 6 augmentation gastro-cystoplasties have been done and their follow-up ranges from 6 months to 3½ years. There have been no postoperative complication and their follow-up studies have so far been satisfactory and uneventful.

Results of Ileocystoplasty for Small Bladder —A Review of 47 cases of Tuberculous Contracted Bladder

By FUMIO TSUCHIYA, MD
SEIZO HORIUCHI, MD
Tokyo Teishin Hospital, Tokyo, Japan

Since 1949 we have performed 77 ileocystoplasties for various diseases, including 47 cases of tuberculous contracted bladder. We herein present the results of ileocystoplasty in these 47 cases. There were 20 male and 27 female. The average age was about 31 years, the youngest was 12, the oldest was 62 years. Of the 47 patients, 28 underwent Scheele's ileal ring plasty and 19 Goodwin's cap or cup-patch method. These patients were followed-up with clinical examinations periodically after operation. During our follow-up, 6 patients died, 3 in hospital and 3 after discharge. Causes of deaths were 1 heart failure, 1 accident, 1 acute and 3 chronic renal failures. Of the 47 patients, 34 were followed up. 25 of them were living uneventfully for more than 10 years and the longest has been surviving well for 26 years after the operation. Of the main complications, urinary fistula in 3 and stricture at the site of anastomosis in 4 were corrected by surgical procedure. 3 patients complained of dysuria and were treated by TUR of the bladder neck. Calculus was observed in 7 cases—1 in the renal pelvis, 1 in the ureter and the other 5 in the bladder.

Most of the patients in our series have not manifested any serious electrolyte aberration if they had good renal function. Before the operation all patients had been suffering from frequency of urination because of a small bladder capacity measuring from 10 to 90 ml. After operation, the capacity of the bladder increased from 300 to 800 ml within several months. The patient, after the operation, voids every 2 or 5 hours in the daytime and 0 to 3 times at night. Most patients with the ring plasty have had from 15 to 100 ml of residual urine. The open-flap method is a little superior to ring plasty regarding the postoperative bladder function. While there are unsatisfactory points to a ring loop procedure, once these patients establish a satisfactory condition for urination, they maintain this condition for 10 or 20 years.

In conclusion, a review of the long-term follow-up of 47 cases suggests that ileocystoplasty is a useful method of treatment for the small contracted tuberculous bladder.

Urinary Diversion: Open Transcolonic Uretero-Sigmoidostomy and Isolated Sigmoid Bladder

By Z. KONDO, MD, Professor; Y. SAITO, MD, Assistant Professor; and K. SHINDO, MD, Instructor

Department of Urology, Nagasaki University, School of Medicine, Nagasaki, Japan

In our clinic the classical uretero-sigmoidostomy was mainly performed for the urinary diversion after cystectomy in patients with bladder cancer from 1950 to 1960, and subsequently the Maculair-Usadel's recto-sigmoid bladder from 1961 to 1968. From 1969 mainly Goodwin-Hohenfelner's open trans-colonic uretero-sigmoidostomy and partly Bricker's ileal conduit were carried out. Recently the isolated sigmoid bladder method was used in some cases.

The classical uretero-sigmoidostomy was gradually abandoned, because many postoperative complications occurred. From 1961 we changed the method to the formation of a rectosigmoid bladder. The sigmoid colon was divided and the descending colon brought out as a cutaneous colostomy. A substitute bladder was made by closure of the distal end of the sigmoid colon. The ureters were anastomosed to the colon by the Mathisen method. In the ileal conduit method the ureters were implanted into the isolated ileal loop by the Nesbit's mucosa-to-mucosa method or Cordonier's method.

Goodwin (1953) presented the open transcolonic uretero-sigmoidostomy, in which the sigmoid colon was incised and the cut end of the ureter was pulled into the intestinal cavity through the mesocolon after an incision in the mucosa of the colon. Subsequently, Hohenfelner (1967) implanted the ureters by means of a submucosal tunnel and cuff formation.

Recently the isolated sigmoid bladder method was tried after simple cystectomy. A loop of sigmoid colon was isolated and the ureters were implanted into this loop by the Hohenfelner's method. The proximal end of the loop was closed and the distal end was anastomosed to the internal urethral meatus.

34 cases have been followed-up, 5 had an ileal conduit, 12 a recto-sigmoid bladder, 13 a transcolonic ureterosigmoidostomy and 4 an isolated sigmoid bladder.

The isolated sigmoid bladder had few complications though 1 patient did have a disturbance in the serum electrolytes. In each of the other methods, pyelonephritis, hydronephrosis and disturbances of renal function occurred in between 30 and 50% of cases.

It appeared that the recto-sigmoid bladder had the highest complication rate whilst the transcolonic ureterosigmoidostomy was marginally better than the ileal conduit with regard to these complications. The recto-sigmoid bladder also was responsible for a disturbance in electrolyte balance in a quarter of the cases.

An Aggressive Approach to Treatment of Bilateral Staghorn Calculi

By DR H. AWANG, LMS (SING), MRCS, LRCP, FRACS

Department of Urology and Nephrology, Hospital Besar, Kuala Lumpur

During the 7-year period from 1968, 22 cases of bilateral staghorn calculi were seen. There were also 36 cases of right staghorn calculi and 25 cases of left staghorn calculi during this period.

All 22 cases with bilateral staghorn calculi had complications. 8 cases had uraemia, and nearly all cases had infection. The majority of the stones were large and long standing, and the complications presented a discouraging clinical picture. Because of the high incidence of complications which could lead to progressive renal damage, an active approach to surgery was adopted. The adopted policy was to remove the large stone surgically, particularly in the presence of infection, and then to treat the infection vigorously. The following principles were followed.

1. Operation was first carried out on the side where the maximum improvement to total renal function could be anticipated with the minimum operative stress.
2. In cases of bilateral obstruction and unilateral infection the infected kidney was treated first.
3. In cases with bilateral staghorn calculi of equal size, operation was first performed on the better kidney.
4. Patients in uraemia were treated by haemodialysis if not responsive to conservative treatment

and surgery was carried out under the protection of haemodialysis.

5. Whenever possible the technique described by Gil Vernet was followed although nephrotomy incisions were sometimes required. The second operation usually followed 3 or 4 weeks after the first.

Surgical removal was undertaken in 17 cases. Of these, 7 required dialysis support. Peritoneal dialysis was used in 2 cases while 5 had haemodialysis. Surgery was performed in 10 cases with bilateral staghorn calculi who were not uraemic.

In the 5 cases who had extensive bilateral operations for the removal of the stones, 2 required nephrectomies later.

All cases had a marked improvement in renal function and infection was controlled. None had gone into renal failure as a result of surgery. Of the 5 cases who had a unilateral operation, 2 were advised against a second operation because of age and cardiac disease. Both improved after operation. 2 cases who were advised a second operation absconded but were well on discharge. 1 case is awaiting a second operation.

From the 7 cases who had surgery under the protection of dialysis 5 had satisfactory results and were weaned off the dialysis. 3 have done well and are still being reviewed. 1 patient died from carcinoma of the liver 3 years after surgery, while another had advanced squamous cell carcinoma of the pelvis found at the time of nephrectomy.

It is concluded that—

1. A large stone must be removed surgically and any urinary infection must be treated vigourously.
2. Renal insufficiency can no longer be considered as a contraindication to operation in bilateral renal nephrolithiasis. Surgery may be performed with the help of dialysis following which an improvement in renal function may be anticipated.

Long Term Result of Nephrotomy

By C. H. LEONG, MBBS(HK), FRCS, FRCSE, FACS

HENRY H. Y. YU, MBBS, FRACS
Queen Mary Hospital, Hong Kong

A total of 498 cases of renal stones were admitted to the University Department of Surgery, Genito-urinary Service from 1966 to 1975. Of these, 72 patients had nephrotomies done for removal of stones. A total of 76 procedures were done for these 72 patients (4 patients had operations on both kidneys).

There were 2 groups of patients:

1. Patients who had a complete kidney bivalve operation of which there were 29 procedures.
2. Patients who had multiple nephrotomies done in association with pyelolithotomies of which there were 47 procedures.

The indications for nephrotomies were large staghorn calculi in 27 cases; large staghorn calculi combined with multiple small stones in 33 cases and multiple stones not completely removable by pyelolithotomy in 16 cases.

In both groups the operation was performed through a loin incision and under normothermia. Occlusion of renal blood flow was limited to less than 30 minutes at any period.

In the first group who had a bivalve procedure, 2 patients developed severe haemorrhage, for which a nephrectomy had to be done in 1 patient while in the other spontaneous haemostasis was achieved in the first 24 hours. 3 patients developed a persistent calycocutaneous fistula and in 2 cases these had to be surgically closed.

In the second group who had a combined pyelolithotomy and multiple nephrotomies heavy bleeding was encountered in 3 cases which in each case subsided with conservative measures.

The long-term functional results were good in both groups. 26 kidneys out of 76 showed a definite improvement of renal function, 47 kidneys showed no obvious changes while 3 kidneys showed only impairment of function. Sterility of urine was achieved in 52 cases. Only 17 patients showed a positive culture after operation. 8 patients in the bivalved kidney group and 18 in the other group showed evidence of residual stones. This obviously can be greatly avoided by using X-ray control during the lithotomy.

The absence of mortality, the low morbidity and the good long-term functional results speak for the use of nephrotomies in selected cases of renal stones.

Ectopic Ureter in Children

By PAUL C. K. YUE, FRCS, FRCS(ED), FACS, DCH
University of Hong Kong, Department of Surgery,
Queen Mary Hospital, Hong Kong

21 cases of ectopic ureter in children were selected to illustrate the three important clinical aspects of ectopic ureter.

1. Ectopic ureter as a cause of wetting in girls when the ectopic opening is below the internal sphincteric zone. This is the commonest presentation of ectopic ureter and 17 cases have been collected in 9 years (1967-1975). These can be divided into 2 groups:

(*a*) Ectopic ureters associated with duplex kidneys

In 9 cases, the upper pole pelvi-calyceal system bearing the ectopic ureter was shown in the intravenous urogram. In 2 cases it was not visualised but its presence was inferred from:

- (i) Lateral displacement of the pelvis and the ureter of the lower moiety.
- (ii) Increased thickness of the renal shadow in the upper pole.
- (iii) Downward displacement of the calyces and decrease in the number of calyces of the lower moiety.

(*b*) Single ectopic ureter

All the 6 cases were associated with dysplastic kidneys. The demonstration of these poorly functioning kidneys was a problem as none of these was shown by intravenous urogram and only 2 were shown by renal angiography using free aortic injection technique. The use of a double contrast technique combining presacral air insufflation with either renal angiography or infusion intravenous urogram succeeded in demonstrating the remaining 4 kidneys.

2. Refluxing ectopic ureters occur in both sexes with urinary infection as the clinical presentation. An

unusual situation in the male was demonstrated in which the ectopic ureter joined the seminal vesicles, with reflux into this whole system.

3. Ectopic ureterocele occurs in both sexes. There are 2 varieties, namely the stenotic and the refluxing type. The latter may prolapse through the bladder neck causing bladder outflow obstruction.

Tuberculosis of the Genito-Urinary Tract

By WILLIAM K. KERR, MD
Toronto Hospital for Tuberculosis, Ontario, Canada

Despite a progressive decline in the incidence of pulmonary tuberculosis, new cases of genito-urinary tuberculosis have continued to appear at the same level for many years. Chemotherapy has reduced the mortality of tuberculosis, from 68% in the 1920s and 1930s to less than 1% today and reconstructive surgery of the genito-urinary tract has succeeded in salvaging many kidneys which would previously have been lost through the development of obstructive uropathy. This report outlines the results of reconstructive surgery in 109 cases of genito-urinary tuberculosis.

During the early 1950s even with good chemotherapy the nephrectomy rate was 40%. Half of these were kidneys which had undergone silent destruction before becoming clinically apparent and had therefore been diagnosed far too late. Others, however, were lost because of progressive obstructive uropathy. Nephrectomy is still indicated for a destroyed non-functioning hydronephrotic or caseous kidney which cannot be usefully salvaged. However, the use of various reconstructive procedures has reduced the nephrectomy rate to under 10% of cases and there is a satisfactory follow-up in 90% of these up to 20 years.

Intrarenal scarring with obstruction of an infundibulum and kinking of the renal pelvis may be corrected by partial nephrectomy and pyelolysis. 26 cases have been so treated and followed up to 18 years. 1 case required secondary nephrectomy at 3 months because of persisting haematuria and renal colic, and 1 case required nephrectomy at 5 years because of pain. The remaining patients are well and free of symptoms.

Speleotomy or cavernotomy involving the deroofing of a tuberculous abscess or closed pyocalyx was performed in 13 cases. In 2 cases urinoma and subsequent urinary fistula occurred, 1 of which closed spontaneously and the other required nephrectomy. In another patient the deroofing of a giant hydrocalyx in a solitary kidney precipitated renal failure and the patient required dialysis. The remaining patients are well.

Strictures of the ureter may progress during the early stages of treatment as scar tissue forms and contracts. If identified early, endoscopic dilatation will usually prove successful in maintaining drainage and there has been little tendency for stenosis to recur once the ureter can be catheterised. The commonest site has been at the uretero-vesical junction. Steroids have been helpful in negotiating impassable strictures. In 39 cases followed up to 17 years, all have done well apart from 1 case who required nephrectomy for pain at 4 years, 1 who required nephrectomy and another who required re-implantation of the ureter for hydronephrosis at 5 years. When dilatation is impossible because of impassable stricture, re-implantation of the ureter has been carried out either by direct anastomosis of the ureter into the bladder (9 cases) or a Boari flap (2 cases) or using a tunnel anastomosis in 3 cases. All 14 cases have done well followed up to 19 years. Open intubation of tuberculous urethral strictures proved unsuccessful in 2 cases in which it was attempted.

Vesical contracture and reflux has been corrected by ileo or colocystoplasty. 17 cases followed up to 19 years provide a panorama of the difficulties involved. There was 1 postoperative death and 1 died later in an accident, the remainder are all living active and useful lives.

Renal and Ureteric Fistulae

By R. B. BROWN, MBBS, FRCS, FRACS
Alfred Hospital, Melbourne, Victoria

A personal series of 73 renal and ureteric fistulae (3 primary, 70 secondary) are presented. The majority of cases were referred.

Surgical causes, often associated with local or general pathology, accounted for 67 of the series whilst external penetrating trauma and primary pathology alone accounted for the remainder.

In an endeavour to determine the possible reasons for such surgical fistulae it was postulated that their development depended apart from the local and/or general pathology present, upon a possible incorrect choice of operation and/or to possible technical faults during the operation.

Certain operations were found to have a high incidence of fistula formation and these included:

Uretero-ureteric renal homotransplantation	27%
Ureteric ligation	25%
Ureter to bowel anastomoses	14%
Partial nephrectomy	12%
Pyeloplasty	9%
Ureterolithotomy for a small calculus in the lower ureter	8%

Retrospective analysis of these particular operations indicated that many uretero-ureteric homotransplantation procedures failed, because of the poor healing qualities of such patients and the disparity in size between the 2 ureters. Often such failure led to the loss of an otherwise well-functioning kidney.

Ureteric ligation may produce a silent renal atrophy, but in 25% of this series the suture blew off the ureter or the kidney extravasated urine through the renal hilum necessitating a secondary nephrectomy.

Ureter-to-bowel anastomoses was found to be more likely to extravasate if the anastomoses were of the direct type rather than a tunnel sub-mucosal type.

When partial nephrectomy was performed for either improving access to the renal pelvis for calculus extraction or because the calyx or calyces involved were only moderately abnormal then this also produced a high rate of fistula formation. It is recommended that partial nephrectomy should not be performed simply for reasons of access nor for moderate abnormalities of the calyces or adjacent cortex.

Many of the fistulae resulting from pyeloplasty operations were felt to be due to an incorrect decision to operate on a congenital upper system dysplasia rather than a localised mechanical or functional pelvi-ureteric obstruction. In addition, it was felt that occasonally the fistula resulted from a wrong choice of pyeloplasty operation even when a definite mechanical or functional pelvi-ureteric obstruction existed.

Assuming that the correct operation has been performed, technical faults may also result in fistula formation and again a retrospective analysis of such techniques were assessed.

In more than half of the cases it was felt, by the responsible surgeon, that poor resistance had contributed to the fistula formation.

There was considerable evidence that the failure to either proximally divert urine or to use a splint in certain situations undoubtedly contributed to the persistence of the fistula.

In 22 cases the ureter was not identified either in its lower or upper region and this was largely responsible for the subsequent fistula.

Several cases, illustrating the importance of detecting and eliminating postoperative distal obstructive causes, were discussed, including unsuspected pelvi-ureteric primary obstruction, ureteric strictures and undetected distal calculi.

Prophylactic measures both before and during operations with a known risk of fistula formation were discussed, including the use of ureteric retrograde catheterisation prior to difficult operations such as those of a secondary or tertiary nature or those in which large pelvic or lumbar masses are present. The decision to operate must be sound and the correct choice of operation must be made. Faults in technique of the type already discussed must be avoided and the question of a possible primary local pathological contribution considered if no other reason for the fistula can be found.

Treatment of the established fistula depends upon type of injury, time of injury, total renal function and pathology, patient's general condition, site of injury, passage of ureteric catheters, life expectancy, surgeon's skill and experience, socio-economic circumstances.

Specific treatment resulted in 87 operations on 70 patients. Because of the inclusion of the uretero-ureteric transplantation group, 21 open secondary repair operations were performed with proximal urinary diversion and Silastic splintage. 16 of these operations were successful whilst 2 required secondary nephrectomy.

15 cases required primary nephrectomy whilst an additional 5 cases required secondary nephrectomy after failure of the initial treatment chosen.

14 cases were treated by retrograde ureteric catheter passage, with or without additional catheter drainage, and of these 11 were successful. Of the 3 failures, 2 required subsequent secondary nephrectomy. 12 cases underwent a uretero-neocystostomy procedure with or without a bladder flap and/or a Psoas hitch operation. 10 of these operations were successful.

Ureteroureterotomy was performed on 6 occasions and all were successful.

9 cases required additional primary abscess drainage and usually urinary diversion whilst 3 cases required additional or associated ureterolithotomy operations. 1 case underwent a successful ileal ureteric replacement and 1 other case underwent a successful renal autotransplantation.

Renal Cell Carcinoma: A Twenty-year Follow up

By Juichi Kawamura, MD, Takuo Iwasaki, MD, and Osamu Yoshida, MD
Department of Urology, Faculty of Medicine,
Kyoto University, Kyoto, Japan

Renal cell carcinoma was reviewed in 106 patients at Kyoto University Hospital. Clinical data was analysed to achieve a better understanding of the natural history of this tumour and to evaluate modes of therapy. A 1- to 10-year survival rate was calculated to determine prognostic factors of this tumour.

Patients were seen most frequently when in their fifties and sixties with the average age of 57·8 years. The ratio of males to females was 3 6 to 1 0 Lateralisation of this tumour was not found. There were no pathognomonic signs in cases of this tumour. However, gross haematuria was present in 74·5%. Only 4 patients (3·8%) had the classic triad of haematuria, flank pain and a palpable mass. Fever of unknown origin was also found in 30%. Among laboratory findings, an elevated ESR was present in 67 1% and the alkaline phosphatase was found to be increased in 33·3%. The metastatic sites of this tumour were varied and the site of distant metastases was most frequently found in the lung (12·3%). Treatment of this tumour consisted mainly of radical nephrectomy including extensive surgery to renal vein and/or inferior vena cave in 100 patients.

The overall relative survival rates were 73% in the 1-year postoperative patients, 46% in the 5-year group and 33% in the 10-year group. There was a good relationship between survival rate and clinical staging of this tumour. Patients in stage D had clearly a poor prognosis at any time and survival rates of those in stages A to C were better than the overall survival rate. Survival rate in stage A was better than rates in stages B and C up to 5 years. However, beyond 5 years there was no difference in the survival rate among stages A, B and C. Patients who had no gross haematuria, but were found to have a palpable mass, fever of unknown aetiology, raised ESR or increased level of alkaline phosphatase were found to have poor clinical courses and prognosis. Those clinical findings may work as prognostic factors indicating the survival rate in this tumour. Long periods of follow-up were required to determine the actual surgical results.

Pelvic Exenteration for Advanced Pelvic Malignancies

By Henry H. Y. Yu, MB, BS, FRACS
C. H. Leong, MBBS, FRCS, FRCSE, FACS
G. B. Ong, OBE, FRCS, FRCSE, FRACS,
FRSE, EPCS(HON), FACS(HON)
Queen Mary Hospital, Hong Kong

A total of 76 pelvic exenterations for advanced or recurrent pelvic malignancies were carried out at the University Surgical Unit between 1964 and 1975. These included 34 cases of malignancies of the female genital tract, 16 cases of malignancies of the lower urinary tract, 23 cases of ano-rectal cancer and 3 cases of sarcoma of the pelvis. Their age ranged from the youngest of 24 years to the oldest of 88 years with an average of 53 years. Bleeding from the primary growth was the most common presenting symptom in this series.

Anterior pelvic exenterations were done in 31 cases where the bladder was infiltrated. Posterior exenteration was done in 21 cases where the rectum was involved. Total exenterations was done in 24 cases.

71% of the cases of advanced malignancies of the female genital tract had previous treatment, mostly radiotherapy and 67% of these cases had clinical recurrence in less than 1 year after the initial therapy. On the other hand, only 6% of the lower urinary tract malignancies had previous radiotherapy. Similarly in the ano-rectal cancer group, only 5% had previous A-P resection. None of the 3 cases of sarcoma of the pelvis had previous treatment.

Urinary diversion in the form of conduits was used in 42 cases of the 55 patients with anterior or total exenterations. All the 12 colonic conduits were done for cases with total exenteration and since 1973, 3 gastric conduits were fashioned for patients after anterior exenterations. A rectal bladder pouch was used in 10 cases while colocystoplasty was done in 3 patients after anterior exenterations for carcinoma of the bladder.

The overall mortality rate for this series was 14%. It was 18% for carcinoma of the female genital tract, 25% for lower urinary tract, 13% for ano-rectal cancer and 0% for the sarcoma of the pelvis group. Eight or 61·5% of the 13 mortalities occurred after total exenteration with septicaemia as the commonest cause. Postoperative complications were high with wound infection, both main and perineal occurring in 24 cases. Urinary fistula occurred in 9 cases. Our experience with the 3 cases of urinary fistulae after colonic conduits showed repair was futile and a second ileal conduit was always required.

The average 5-year cumulative survival rate in this series was 20%. It was 44% for the lower urinary tract malignancies as compared to 17% for female genital cancer and 21% for ano-rectal cancer. None of the 3 cases of sarcoma of the pelvis survived for more than 1 year. Follow up of 37 cases who died over the years showed 78% died from secondaries and 6% died from progressive renal failure. 7 cases in this series have survived for more than 5 years and remained tumour free. Our experience with 76 pelvic exenterations showed that this procedure was not only feasible for advanced or recurrent pelvic malignancies but also could be life-saving in some of these cases which presented with protracted bleeding.

The Urethral Syndrome

By A. J. SPLATT, MS, FRACS
Department of Surgery, University of Queensland

Recurrent dysuria in females is thought to be due to bladder outflow obstruction as the result of fibro-elastosis of the distal half of the urethro-vaginal septum. The normal smooth muscle which is intimately associated with elastic tissue in this area is absent, the elastic tissue becomes clumped, and, in advanced cases, there is intrusion of collagen. These changes result in a mismatch between urethral compliance and bladder power so that varying degrees of bladder outflow obstruction occur.

The symptoms of frequency, hesitancy, an interrupted stream, post-micturition dribbling, and, in advanced cases, of the need to strain to urinate, are indicative of bladder outflow obstruction or of a weak detrusor. The latter is excluded by a neurological assessment or by absence of drug therapy which has an anticholinergic effect.

The degree of obstruction is ascertained by the flow rate, the degree of bladder trabeculation and the amount of residual urine.

The flow rate is measured by instructing the patient to measure the amount of urine passed at any one time and the number of seconds it takes to do this—and this is done several times. The patient is given a chart to fill in at leisure and in familiar surroundings. A flow rate which is persistently below 20 ml per second is regarded as abnormal.

Using these criteria, 34 patients were subjected to a Richardson (1969) urethroplasty, and in all there was an improvement in the flow rate and the symptoms. All had histological evidence of fibro-elastosis. There were no cases of incontinence following the operation.

It appears that the condition of fibro-elastosis is common and that it could well account for the high rate of cystitis in females either directly or by virtue of the fact that the symptoms to which it gives rise tend to mimic those of cystitis.

Changing Pattern of Urological Diseases in Hong Kong

By C. H. LEONG, MBBS(HK), FRCS,
FRCSE, FACS
G. B. ONG, OBE, MD, FRCS, FRCSE, FACS,
FRACS
Queen Mary Hospital, Hong Kong

There has been a definite change in the pattern of urological problems in Hong Kong over the last two decades. In calculous disease, vesical stones appear to proceed towards extinction while the incidence of both renal and ureteric stones has remained high. This could well be explained by the improvement in socio-economic background where better nutrition has prevented the development of hypovitaminosis A and thus avoided excessive bladder mucosa desquamation. In the realm of malignant diseases there has been a marked increase in bladder cancers since the middle of the 1960s. This appears to follow closely the economic boom in Hong Kong, where the textile industry tops the list. Dye chemicals may therefore be the basic cause. Tuberculosis of the urinary tract is still endemic and the incidence has actually increased in the last 10 years in spite of a progressive decrease in pulmonary tuberculosis. Prostatic disease which was at one time a rare entity amongst local Chinese has increased many times in the last decade. This could well be attributed to the lengthening of life expectancy in the local population. Renal vascular lesions causing hypertension also appear to be on the increase.

Many other aetiological factors probably come into play. Better education of the public has led to some urological diseases coming to light in an early stage whereas in the past such diseases may never have been apparent. The development and recognition of genito-urinary specialisation; a better diagnostic know-how; and the availability of a local dialysis unit as a support adds a great deal in the early establishment of proper diagnosis and better treatment.

The patterns of management of various urological problems have shown many changes. In general it can be said that an increasingly conservative management is applied to benign lesions while more radical endeavours are the treatment of choice in malignant diseases. Work bench surgery where indicated is becoming more popular.

Phaeochromocytoma of the Bladder

By I. F. Potts, MS, FRCS, FRACS
Sydney Hospital, Sydney, NSW 2000

This is probably more correctly described as a paraganglioma. Paraganglioma in the bladder are rare tumours and approximately 61 cases have been described in 1975, since the original report in 1953. Of these, 6 cases were malignant. Multiple tumours may represent either multi-focal origin, recurrences or metastasis. The sex ratio is fairly even and the age of onset from childhood to old age, with predominance in the fourth decade. Haematuria is present in about 50% of the cases. The pathognomonic history for a bladder tumour is the complaint of headache, dizziness, tachycardia and sweating, either when the bladder is full or at the end of micturition. Cystoscopy fails to show a tumour in about 20% of cases as the tumour tends towards the outer layers of the bladder wall. There has been no report of a correct cystoscopic diagnosis. Hypertension may be paroxysmal, fixed or absent. Estimation of urinary VMA and urinary free adrenalin and free noradrenalin is positive in about two-thirds of cases. Estimation of blood catecholamine levels may be done via vena caval catheterisation at various abdominal levels.

The case report involves a caucasian male aged 56, seen in April 1968 with painless haematuria. For the past 6 months following urination in the morning; he had severe headache for 3-4 minutes. An IVP showed normal upper tracts with a filling defect in the cystogram on the right side. Cystoscopy confirmed a tumour in this site 2 × 2½ cm and sessile. There was superficial necrosis, some phosphatic deposits on the surface and marked bullous oedema. It was clearly defined. The tumour was impalpable on bimanual, and a biopsy was taken which was reported as a phaeochromocytoma associated with cystitis cystic and marked superficial oedema. The urinary cathecholamines were slightly raised. In May 1968 the tumour was removed by partial cystectomy. It was raised about 1 cm about the adjacent bladder wall and had a well-defined edge. It was not unduly vascular, no draining lymph nodes were palpable.

Manipulation of the tumour produced marked elevation in the blood pressure which was controlled with i.v. phentolamine. The hormonal study of the tumour itself was very interesting showing 7,700 μg/g of wet tissue of adrenalin and noradrenalin indicating a tumour of very high catecholamine storage capacity. There has been no sign of recurrence in an 8-year follow-up and his urinary catecholamines remain normal. Phaeochromocytomas have been described in association with a wide variety of other tumours of unrelated tissues. These include medullary thyroid carcinoma, parathyroid adenoma, Hippel-Lundau disease and generalised neurofibromatosis and an association with renal cell carcinoma has also been noted. The prognosis is good for non-malignant phaeochromocytomas and is better in malignant tumours of the bladder than for malignant tumours in classical sites.

Diathermy to the Trigone and Urethra in the Management of the Female Urethral Syndrome

By J. S. Taylor, FRCS, FRACS
Royal Newcastle Hospital

This paper presents 2 studies on the effect of diathermy in the treatment of the female urethral syndrome.

The first study is a randomised controlled trial involving 27 patients. The follow-up period was 6 months. Those patients who had diathermy applied to the trigone and urethra had significantly fewer attacks during the 6-month period of follow-up than those who only had cystoscopy performed.

The therapeutic trial was of 56 patients. All patients were followed up for a minimum of 3 years. At the end of that time 45% had no further attacks from the time of diathermy, and 45% more considered that the treatment had benefited them. There were no significant complications or side-effects. The major disadvantage appears to be dysuria and increased frequency of voiding for several weeks following the diathermy. This mode of treatment appears to be superior to other forms of treatment at present practised.

Open Renal Biopsy

By I. N. Nunn, MBBS, FRCS, FRACS
Royal Melbourne Hospital, Melbourne, Victoria

Percutaneous needle biopsy of the kidney has resulted in a vast increase in the knowledge of and the treatment of renal disease.

Complications occur even in the hands of the most experienced of operators, and are most commonly related to bleeding. The percentage of complications varies from centre to centre, some very high, and even in the best of hands the nephrectomy rate is 0·1%.

The major factors affecting the complication rate are the experience of the operator and the depth of the biopsy. The very vascular tissue at the cortico-medullary junction are most easily damaged.

It follows that there are increased risks to needle biopsy when the cortex is thin or irregularly scarred. Experience has also shown that patients with severe hypertension or uraemia have a high complication rate.

A technique of open renal biopsy was described and the results in 51 patients discussed. There was a low complication rate and open renal biopsy is advocated in those patients requiring a biopsy who have a solitary kidney, small or coarsely scarred kidney, congenital anomalies of shape and position, a thin renal cortex, severe hypertension and severe uraemia of unknown cause.

Vesico-colic Fistula due to Diverticulitis

By H. G. WATTS, FRCS, FRACS
Tauranga Hospital, Tauranga, New Zealand

From 1965 to 1974, 7 men aged 46 to 76 with vesico-colic fistula due to diverticulitis were admitted to Tauranga Hospital, New Zealand. 6 presented with pneumaturia and in all patients urinary symptoms were predominant and bowel symptoms were not striking. 5 had a pelvic mass.

The diagnosis was made largely on the history and by finding localised cystitis, localised bullous oedema or the actual fistula on cystoscopy. 1 fistula was demonstrated on a cystogram and all bladder contours were distorted by the thick, adherent sigmoid. All barium enemas showed diverticulitis, but none outlined a fistula.

All 7 patients were treated by primary resection of the affected colon and closure of the bladder defect without a preliminary colostomy. 1 man who was partly obstructed had a colostomy fashioned at the time of his resection. This was closed 2 weeks later.

The technique of colonic anastomosis is important. Tension must be avoided. A good blood supply is essential. These anastomoses were done in 1 layer using a catgut allcoats running suture. No clamps were placed on the bowel ends.

There were no deaths in this series and little morbidity. No anastomotic leaks occurred. The average postoperative hospital stay was 13 days. All patients have remained well in the follow-up period.

Colostomy prior to resection does not lead to spontaneous closure of a vesico-colic fistula and does not lessen inflammation in the diverticular colon. It is suggested that a 1-stage resection anastomosis without colostomy is a safe and effective management for vesico-colic fistula provided that gross pelvic sepsis or obstruction do not co-exist and that the colonic anastomosis is technically satisfactory.

A Lymphographic Study on Chyluria

By H. NGAN, MBBS, MRCP, MRCPE, FFR, DMRD
Hong Kong

Bilateral pedal lymphography was performed on 67 patients with chyluria. The pelvic and para-aortic lymphatic vessels were increased in number, tortuous and dilated in 42 patients. There was reflux of the contrast medium to the renal lymphatic in all but 2 of the patients: 23 on the left, 12 on the right and 28 bilaterally. Contrast medium was also present in the left calyceal system in 18 patients, in the right calyceal system in 8 patients, in both calyceal systems in 2 patients and in the bladder in 12 patients. The lymph nodes were small and/or sparse in 32 patients, enlarged in the para-aortic regions in 8 patients and normal in 27 patients.

Postoperative lymphography was performed on 14 patients after stripping of the lymphatics at the renal pedicle. Of the 12 patients who had had unilateral stripping by the retro-peritoneal approach, all showed absence of reflux of the contrast medium to the ipsilateral kidney. Of the 2 patients who have had bilateral stripping performed during the same session, persistent reflux of the contrast medium to the left renal lymphatics was present in both patients after surgery.

Plasma Renin Concentration in Hypertension Produced by Unilateral Renal Artery Constriction in the Rat

By H. OATES, MBBS
B. G. STOREY, MBBS, FRCS, FRACS
G. S. STOKES, MD, MRACP
Sydney Hospital, Sydney, NSW 2000

Hypertension produced in rats by constricting 1 renal artery represents the counterpart of clinical unilateral reno-vascular hypertension.

Therefore this model has been studied frequently to determine whether the renin-angiotensin system plays an essential role in the pathogenesis of the hypertension produced.

Nevertheless the issue still remains in doubt.

In this study we measured the plasma renin concentration and blood pressure at intervals for 42 days following unilateral renal artery construction to determine whether increases in plasma renin concentration bear any relationship to the development of hypertension.

METHOD

Female Wistar rats weighing 250 grams maintained on a standard laboratory diet and tap water were used.

3 control measurements of the plasma renin concentration, B.P. and the body weights before renal artery constriction were carefully recorded.

Under ether anaesthesia a silver clip of 0·25 mm internal diameter was applied to the left renal artery of each rat.

Systolic B.P. was measured using a photo-electric cell and a proximal cuff around the tail of each conscious pre-warmed rat. P.R.C. was measured by radio-immuno assay of ^{A}I generated after incubating plasma samples at pH 6·5 with excess rat renin substrate.

Postoperative Schedule]

A blood sample for plasma renin concentration determination was obtained from each rat between 10.30 and 11.30 a.m. to avoid diurnal variation, and the blood pressure was recorded 3 hours later. Thus P.R.C. and B.P. were recorded sequentially for 42 days. Each rat was re-weighed at the end of the experiment.

Results were as follows: 25 of the 53 rats remained normotensive, P.R.C. did not rise at all and the body weight did not alter. Only 22 of 28 rats which became hypertensive survived the duration of the experiment. In these 22 rats the mean P.R.C. rose significantly on day 3 before the B.P. had commenced to rise.

P. R. C. continued to rise until it reached a maximum on day 14. Maximum B.P. was not reached until the 35th day. In 11 of these hypertensive rats P.R.C. did not rise significantly above the normal during the experiment.

In the other 11 rats P.R.C. rose dramatically to a maximum 5 × the normal. However, the P.R.C. increases did not show a clear temporal relationship to B.P. changes.

DISCUSSION

The results obtained by sequential sampling show that the mean P.R.C. rose progressively in the hypertensive rats from day 3, reaching a peak at day 14, which coincided with the establishment of hypertension following unilateral renal artery constriction. Linear regression analysis of the log P.R.C. versus B.P. values compiled from all 22 hypertensive rats over the whole 42 days revealed a highly significant correlation between the 2 parameters. Nevertheless it appears that P.R.C. was not the only, or even the most, important factor in producing the hypertension because:

1. No significant correlation between P.R.C. and B.P. arose until the 35th day.
2. Mean P.R.C. and B.P. in the 22 hypertensive rats showed no consistent temporal relationship in individual rats.
3. 11 of the 22 rats did not exhibit a rise in P.R.C. at all.

IN CONCLUSION

Since 11 of the 22 rats which developed hypertension following unilateral renal artery clipping showed no elevation of P.R.C. at any stage, this form of hypertension does not arise solely from increased levels of circulating plasma renin. However, in the overall analysis the log P.R.C. and B.P. were related to a highly significant degree. Whether this relationship was a result or cause of hypertension cannot be established from the present data.

Carcinoma of the Upper Urinary Tract associated with Analgesic Nephropathy

By B. G. STOREY, MBBS, FRCS, FRACS
J. F. MAHONY, MBBS, FRACP
J. H. STEWART, MB, CHB(NZ), MRACP, MRCP
Sydney Hospital, Sydney, NSW

Phenacetin, an aromatic amide derived from analine, has been ingested by man for more than one hundred years.

In 1895 Rehn described the carcinogenic properties of the aromatic amides on the urothelium. Spuhler and Zollinger in 1953 reported the association between papillary necrosis and analgesic abuse.

Haltegren *et al.* of Sweden in 1965 first suggested an association between analgesic nephropathy and carcinoma of the renal pelvis. Since then there have been reports of more than 60 additional cases of analgesic associated carcinoma of the urothelium in Sweden alone and some 30-odd cases from the rest of the world, mainly in Australia, Switzerland and West Germany.

In all these cases the analgesic taken contained phenacetin and caffeine, and at least 1 other substance, usually phenazone in Sweden, aspirin in Australia, and in most there was histological or radiological demonstration of papillary necrosis in the kidney adjacent to the tumour

In Huskvarna, a Swedish town of 13,000 inhabitants who are mainly machine workers with free access to A.P.C. powders and tablets from 1918 to 1960, consumed 1·4 million A.P.C. powders in 1959 containing 700 kg of phenacetin.

Since 1961, 26 new cases of primary carcinoma of the renal pelvis have been reported.

Stewart Taylor in 1972 found the evidence of carcinoma of the renal pelvis in kidneys damaged by analgesic nephropathy to be 9 times greater than in those damaged by inflammatory disease alone.

Between August 1971 and February 1976, 18 new cases of primary carcinoma of the renal pelvis and 2 of the ureter were treated at the Sydney Hospital.

11 of the patients with carcinoma of the renal pelvis and 1 with ureteric carcinoma gave a history of prolonged and heavy analgesic intake.

6 patients had taken BEX powders, 2 to 12 per day for between 5 to 30 years, 5 took BEX or Vincents powders in similar amounts. The twelfth patient, who suffered from rheumatoid arthritis, had taken 6 to 12 tablets a day, either Veganin or Burco for over 30 years.

All were female except 1 patient who was a policeman; 10 of the 11 women were housewives, the other a bookstall employee.

The presenting symptoms were macroscopic haematuria in 17 of the 20 patients, flank pain in 2 and gout and renal failure in 1.

7 of the 8 non-analgesic cases had normal serum levels of creatinine and there was no rise after nephrectomy.

In contrast, 8 of the 12 analgesic habitués had elevated serum concentrations of creatinine and in 3 there was a further rise following nephrectomy.

All patients underwent operative removal of the tumour except 1 from each group with hepatic metastases at the time of diagnosis. The tumour was transitional cell carcinoma in all cases. 11 patients have died, 9 from metastatic cancer in liver and/or bone and 2, both from the analgesic group, of renal failure. 1 of these had a second tumour in the contralateral renal pelvis. Maintenance dialysis therapy has been necessary for a third patient with renal papillary necrosis who has developed end-stage failure.

Survival was worse in those with analgesic nephropathy. 5 patients had developed associated carcinoma of the bladder, 4 of these occurred in patients in whom the lower ureter had not been removed.

The association between analgesic abuse, renal papillary necrosis and carcinoma of the renal pelvis suggests that phenacetin is carcinogenic for uroepithelium.

New metabolites of phenacetin have recently been found in urine of humans and animals, the N-hydrooxylation products seem to be nephrotoxic and carcinogenic. The excretion of these products is increased by the ingestion of barbiturates, phenozone, caffeine and smoking.

Intrinsic Urethral Resistance

By G. F. MURNAGHAN, MD, CHM, FRCS
S. P. GOWLAND, MB, CHB, FRACS
MARGARET ROSE, BVSC
A. LALAK, MBBS, FRCS
The University of New South Wales, Sydney, NSW

Urethral pressure profiles have been studied in a series of 13 female pig-tail monkeys (*Nemestrinas macaca*). Control profiles were taken at different depths of ketamine anaesthesia and during deep halothane anaesthesia for laparotomy or pelvic exploration, and stable reproducible profiles were obtained under these experimental conditions in individual animals.

In 4 animals the changes in profile were evaluated after spinal cord section with demonstrable reflex neurogenic bladder disorder and in 3 animals after cauda equina section with autonomous neurogenic bladder disorder. In the remaining 6 animals of the series, profiles were obtained before and during stimulation of either the presacral nerve or pudendal nerve and then during pharmacological blockade or stimulation of the autonomic or somatic components of the nervous system.

Significant variation from the normal profile did not accompany experimental spinal reflux or autonomous neurogenic bladder disorder.

Augmentation of the normal mid-urethral profile peak was noted to follow either presacral nerve stimulation or the administration of a-adrenergic drugs (noradrenaline), but this augmentation could not be obtained by either stimulus during a-adrenergic blockade with phentolamine. The stimuli were not accompanied by any increase in the amplitude of the urethral pressure profile at the bladder neck or proximal urethra.

Difficulties were encountered in monitoring the dosage of b-adrenergic stimulatory and blocking drugs and suxamethonium chloride.

Electrostimulation of the pudendal nerve produced a high peak profile with some shift towards the bladder neck and with variable blockade of this effect by suxamethonium chloride and phentolamine.

These studies suggest that intrinsic urethral resistance in the monkey is under significant motor influence of the autonomic nervous system. A preliminary suggestion that such autonomic innervation may be distributed through the pudendal nerve requires further evaluation.

These studies were supported by a grant-in-aid from the Australian Kidney Foundation.

Transvaginal Closure of Vesicovaginal Fistulae

By ROGER BARNES, MS, MD, DSC
Professor of Urology, School of Medicine
Loma Linda University, Loma Linda,
California, USA

Attempted closure of vesicovaginal fistulae has often failed. When the suprapubic approach is used, hospitalisation is often prolonged and sometimes the patient is kept in bed in the very uncomfortable prone position for many days.

For 30 years we have used the transvaginal approach for repair of most vesicovaginal fistulae.

Contraindications to the transvaginal approach. (1) large fistulae more than 4 cm in diameter; (2) very small vagina; (3) rigid tissue due to excessive fibrosis and/or radiation reaction; (4) combined vesicovaginal and ureterovaginal fistulae.

Technique of the transvaginal approach. The patient is placed in the inverted lithotomy position, *i.e.* face down with the thighs flexed and abducted over the lower end of the table. The knees are flexed and legs are held in an abducted position with a sheet placed around each knee and fastened around an upright of each side of the table. In this position the field of operation is on the floor, rather than on the ceiling where it is when the patient is in the conventional lithotomy position.

The perineum is retracted, preferably with the posterior retractor used during perineal prostatectomy. A Gelpi retractor separates the labia. An incision is made through the anterior vaginal wall for a distance of 1½ to 2 cm both above and below the fistula and around the fistula at the junction of the vaginal with the bladder mucosa. From this incision the vaginal mucosa is separated from the bladder for a distance of 1½ to 2 cm on all sides of the fistula. Closure is made in 5 layers using 3-0 chromic or Dexon sutures. Each layer is continuous. The first layer inverts the bladder mucosa; the second approximates the under surface of the bladder wall; the third approximates the lateral angles of the dissected area; the fourth approximates the under surface of the vaginal mucosa and the fifth is submucous to the vaginal mucosa. Each layer of suture covers the preceding layer. Thus, a thick mass of tissue is built up between the vagina and the bladder. A catheter is left in the bladder through the urethra for continuous drainage and a 2-inch pack is inserted into the vagina.

Postoperative care. The vaginal pack is removed and the patient ambulated on the first postoperative day. The catheter is removed on the third postoperative day and the patient leaves the hospital on the fourth or fifth day in most cases.

Results. During the past 30 years we have done 80 cases by this technique, with 87% successful permanent closure after the first attempt and 95% after the second closure done by us. Many patients had had previous attempts elsewhere to close the fistulae; one had had 8 previous unsuccessful operations. No patient had urinary incontinence following closure of the fistulae.

Pathophysiological Damage to the Kidney due to Temporary Ischaemia and its Prevention

By PETER H. PETRITSCH, MD
PETER VILITS, MD
HERBERT LIPSKY, MD
Department of Urology, University of Graz, Austria

In recent years organ and tissue-saving surgical procedures have become increasingly important in a variety of renal diseases. In many instances this type of renal surgery necessitates the interruption of renal circulation which can of course lead to kidney damage.

Protracted periods of ischaemia impede normal cell metabolism, which subsequently leads to an accumulation of anaerobic waste products mainly in the renal cortex. These waste products in combination with anoxaemia are responsible for tubular necrosis. Our results and those of other investigators show that a lack of post-ischaemic blood flow is one of the main reasons for ischaemic kidney damage. Even after restoration of the renal circulation ischaemic damage continues because the capillary flow is inadequate, thus resulting in further anoxaemia and reduced elimination of anaerobic waste products. This could be observed in every instance of renal ischaemia between 80 minutes and 3 hours in the animal experiments. The kidneys were swollen and congested. Histological examination demonstrated a severe parenchymal and endothelial oedema, which caused an obstruction of renal capillaries. These histological findings were at least in some instances confirmed by previously performed angiograms. In every case we observed several degrees of tubular cell degeneration shortly after restoration of renal blood flow, which finally resulted in almost complete tubular necrosis 24 hours later. The reason for cell swelling is the lack of energy supply during the ischaemic period, because the maintenance of the intracellular fluid balance is an energy requiring process.

In order to find a practicable method of protecting the kidney from the otherwise lethal effect of protracted periods of normothermic ischaemia we have evaluated several pharmacological agents, with respect to their protecting capacity. Only mannitol proved to be of significant value avoiding cell-swelling, if given 3-5 minutes prior to the interruption of renal circulation.

If longer periods of ischaemia can be expected we prefer to apply a method of kidney preservation described by Sacks, Petritsch, Leong and Kaufman. This allows time enough to perform any kind of meticulous surgery either *in situ* or extracorporeal, even under an operating microscope. (Case presentation.) This method combines the well-known beneficial effects of hypothermia and of hyperosmolar intracellular electrolyte solution.

As a result of our investigations we believe that an important factor in avoiding ischaemic damage lies in guaranteeing sufficient postoperative renal blood flow. This seems to be at least partially successful when the hyperosmolar kidney preservation methods are used.

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Book Reviews

Pathological Basis of Renal Disease. By M. S. DUNHILL. Pp. vii+473. London: Saunders, 1976. £17·50.

The author covers the pathology of those diseases in which renal biopsy is of value. Thus he omits congenital abnormalities, functional tubular disorders and consideration of tumours. The urologist beginning to lose interest at this point should persist, since there are excellent chapters on renal infection, papillary necrosis, transplantation and hypertension. However, this is a book mainly for pathologists and renal physicians, covering the field of parenchymal renal disease in some 30 chapters, each terminating in a list of key references.

In recent years a number of valuable texts on renal pathology have been produced by expatriate Britons. Dr Dunhill is to be congratulated on producing a most useful work without leaving these shores, particularly since he has a considerable reputation in unrelated fields of pathology. Without attempting the encyclopaedic breadth of Heptinstalls' "Pathology of the Kidney" the author has covered most of the questions which arise with a difficult renal biopsy. His review of the literature on the illusive haematoxophil body of lupus nephritis is particularly interesting. A minor point of criticism is the perpetuation of the term "membranoproliferative" with its suggestion of a relationship to idiopathic membranous glomerulonephritis, rather than the widely used "mesangiocapillary" glomerulonephritis.

Although lacking a dust cover the quality of production is excellent. Micrographs are informative and of a size which allows critical scrutiny. As befits their importance considerable use is made of both immunofluorescence and electron microscopy. The latter are of high quality but occasionally suffer from poor reproduction.

In summary, this is an excellent book which will be of value to both the diagnostic histopathologist and the clinical nephrologist seeking a balanced account of the pathology of renal disease. At a cost of £17·50 it can be regarded as an investment. A. M.

The Sexual Experience. Edited by BENJAMIN T. SADOCK, HAROLD I. KAPLAN and ALFRED M. FREEDMAN. Pp. xiii+666. Baltimore: Williams and Wilkins, 1976. $23.50 (£14·10).

Neither the title nor the tenderly erotic Rodin cover illustration should mislead the potential reader to expect yet another addition to the increasing volume of porn which masquerades in pseudoscientific guise. Far from it—this is a comprehensive and academic textbook edited by three eminent American professors of psychiatry.

Written for the professional reader as well as for the inquisitive man (or should one say, person) in the street, this volume covers every aspect of human sexual behaviour. Its 48 contributors discuss topics which range from the anatomy and physiology of sex to developmental, functional and social aspects. Unique to a book of this kind is a detailed description of the techniques of coitus, a subject which is conspicuous by its absence in most medical educational programmes.

Many other topics such as abnormal sexual behaviour, advances in the treatment of sexual disorders, as well as sociological issues relating to sexual behaviour and marriage, the problems associated with contraception, abortion and sterilisation, are fully discussed.

There is an unevenness which is perhaps inevitable in an anthology of this kind, but the book is full of surprises and new knowledge. For instance, the reviewer had no idea that in the United States there were no fewer than seven recognised-types of prostitution establishments, which only supports the view expressed in the preface that sexuality is one of the most intriguing subjects in the area of human behaviour!

At a cost of $23.50 (£14·10) this book is good value. K. S.

Fundamentals of Urology. Edited by J. LAPIDES. Pp. 540. Philadelphia: Saunders, 1976. £13·00.

In 1942 Nesbitt published a textbook of urology for medical students. Long out of print after 4 editions in 10 years, it has now been brought up to date, under the editorship of Lapides, with 22 contributors. A series of 20 monographs gives a comprehensive introduction to urology and a secure foundation to the student who masters its contents. Accounts of the basic anatomy, physiology and pathology of the urinary tract are clear and concise, though inevitably incomplete in a book of this nature. However, they are good reminders of information which the student will have learnt elsewhere in more detail. Sections on clinical urology are mostly good summaries of current urological practice, although there is some inconsistency in the amount of detail, particularly operative, which is sometimes mentioned in outline only, or on other occasions even mentions the gauge of catgut to be used.

A number of inadequacies are to be found. An informative section on uroradiology devotes too much space to the cost of various investigations, but barely mentions nephrotomography and is wholly inadequate in the use of radiology as a functional investigation. Isotope studies are barely mentioned and there is no reference to sonography. Pelvi-ureteric obstruction is summarily dismissed with no discussion of the very important research relating to its pathogenesis and diagnosis A half-page of rather dogmatic assertions on the treatment of carcinoma of the prostate is surely not enough.

A medical student returning from outpatients may want to look up something about the problems he has seen; it would be helpful to have a concise summary of haematuria, the differential diagnosis of renal pain, or the interpretation of bladder symptoms. In common with most urological textbooks he will find little help in sorting out the most common problem of all: the patient with "bladder symptoms".

These criticisms relate to the sort of detail which might be made of any textbook. There is, however, one particularly disappointing section in an area which urologists have made peculiarly their own. The chapter on the physiology of micturition and cystometry is quite inadequate. An obsolete method of cystometry is described and the measurements of flow-rate and urethral profile are ignored. The impression is given that detrusor dysfunction is entirely neuropathic in origin—which may be true, but is certainly arguable. The application of urodynamics to the problems of incontinence and outflow obstruction are almost wholly ignored.

Provided the student is instructed to read some parts of this book with caution, he will find it an excellent and comprehensive survey of urology. D. M. E.

The Kidney. Edited by B. M. BRENNER and F. C. RECTOR. Pp. 1948. Philadelphia: Saunders, 1976. £55·00.

This is a well-illustrated multi-author book in two volumes The editors have succeeded in their aim of giving a strong foundation in renal physiology and pathophysiology in Volume I. In Volume II the book suffers a little from the duplication which is inevitable with multiple authors. However, in several instances the "second opinion" was invaluable in protecting the reader from the overenthusiastic claims of other chapter authors Thus Dr Najarian and his co-authors give the impression that the use of anti-lymphocyte globulin (ALG) is essential for successful transplantation; a balanced review of the evidence by Dr Thier's group in a later chapter comes to the more generally accepted conclusion that the value of ALG is uncertain in the human situation. Dr Belzer can "quite simply . . . distinguish tubular necrosis from rejection" by radioscintiphotography, Dr Thier makes it quite clear that the rest of us do not possess this gift. Because of these and other instances of misleading statements arising from a rather dogmatic approach in some chapters, which are otherwise excellent, the reader not experienced in clinical nephrology should take advantage of the "second opinions" available in the book. Apart from these minor criticisms the clinical section, like that on physiology, is excellent with up-to-date contributions from leaders in their fields. Although this is a large book the chapters have been written to be read in their entirety as well as for reference; each gives the pathophysiological background to its subject before proceeding to clinical aspects and much is lost if the parts of the chapter are read in isolation. The chapters have extremely comprehensive bibliographies which will be very useful to those engaged in or embarking on research in nephrology.

This book can be strongly recommended to physicians training or working in nephrology, to surgeons engaged in renal transplantation and to renal physiologists. It should also be available to non-specialists in departmental libraries.

R. W.

Clinical Pediatric Nephrology, First edition. Edited by E. LIEBERMANN. Pp. 587. Philadelphia: Lippincott, 1976. £31·20.

This book is well titled; it is intended for the clinician. Renal anatomy and physiology do not occupy several long chapters in an early section of the book, doomed to lifelong neglect by most clinicians, as is customary in renal textbooks; they are dealt with briefly and the descriptions are woven into the chapters on clinical topics. The aim of the editor has not been to provide a comprehensive textbook of nephrology, organised on disease systems, but to describe the diagnostic work up of children with common presenting symptoms and signs—hypertension, proteinuria, haematuria, etc.—and the management of the major renal diseases. He has assembled a group of well-known authors including Gavin Arneil on nephrotic syndrome, Jean Smellie and Ian Norman on pyelonephritis, Martin Barratt on hypertension, Robert Whittaker on congenital abnormalities, Cyril Chandler on renal function tests in children, and Renee Habib on renal biopsy from this side of the Atlantic.

The first 8 chapters are devoted to the investigation of symptoms and signs. They are set out clearly and simply with step-by-step plans of action. At times they strive too hard for completeness and overstress the rare—for instance a chapter on growth retardation lists progeria, leprechaunism, gargoylism, and cri-du-chat syndrome but makes no mention of social and emotional deprivation which seem to be the commonest causes of retarded growth in this country. This appears to be part of the defensive approach to medicine forced upon our American colleagues by their legislative climate: renal biopsy is "absolutely contraindicated" in a single kidney; there are no suggestions for ever discharging the child with orthostatic proteinuria from follow-up. In contrast, Professor Arneil is in favour of managing many children with nephrotic syndrome without hospital admission.

The chapters on the major syndromes and two interesting accounts of renal function tests in childhood and the interpretation of renal biopsy are all balanced and well-written accounts. There are a few unsupported recommendations ("prednisone should never be given without vitamin D") and the usual smattering of errors in a first edition ("urates discolour the urine", "bicarbonate excretion is raised in renal failure", "prednisone suppresses aldosterone", etc.), but in general it is a scholarly account with a good index and plentiful references to the original literature and above all it is pleasant to read and in excellent readable type. With these advantages one cannot hope for a price below 5p a page in 1977.

D. N. S. K.

Renal Pathophysiology. By ALEXANDER LEAF, M.D, and RAMZI COTRAN, MD. London: O.U.P., 1976. £5·00.

If I were appointing a Consultant Nephrologist and I had to choose between one who was well schooled in renal physiology and another who had studied surgery, obstetrics, general medicine, neurology, cardiology, etc., I would pick the latter. Clinical nephrology is still remarkably divorced from the basic renal sciences. However, this is bound to change in the next few years and many middle-aged nephrologists and urologists must feel the need to catch up on what is happening in the basic sciences. This relatively short, readable book, in a print that can be read without bifocals, should prove an excellent introduction and at £5·00 it is one of the few books I have recently reviewed which can be recommended for personal rather than library purchase. The areas in which there is already a happy dependence of clinical practice on basic science are well covered, *e.g.* the appearances of renal biopsies on light fluorescence and electronmicroscopy, their relationship to clinical features, and to a limited extent, to treatment: the pathophysiology of chronic renal failure: the causes of oedema and the action of diuretics: potassium excess and deficiency. Acid base regulation, as usual in such books, receives a very sizeable allocation of space. It is written in a very traditional style and I found it quite comprehensible (which is unusual for descriptions of acid base regulation). There is a chapter on calcium, magnesium and phosphate which should be largely revision for urologists and an interesting chapter on the interpretation of the serum sodium concentration.

Not exactly bedtime reading but less soporific than most books that instruct in basic science; I recommend it for young as well as middle-aged students of nephrology and urology.

D. N. S. K.

Dialysis, Transplantation, Nephrology. Proceedings of the European Dialysis and Transplant Association, Volume 13. Edited by B. H. B. ROBINSON, P. VEREERSTRAETEN and J. B. HAWKINS. Pp. 655. London: Pitman Medical, 1977. £19·50.

To assemble 67 manuscripts from 16 countries and 4 continents, edit them, tidy the English, transcribe and shorten the discussions and produce an attractive volume within 5 months of the conference is an awe-inspiring feat; the editors and publishers deserve congratulation. The book starts with 100 pages of statistical reviews, giving detailed information on more than 20,000 European patients treated by dialysis and transplantation with a shorter analysis of experience in the rest of the world. These EDTA annual reports are much the most informative descriptions of the treatment of renal failure available and have become the standard source of information for government planners. They are followed by a review article—this year by Thomas on uraemic neuropathy.

The main body of the Proceedings—the papers given at Hamburg 1976—cover the clinical results, complications and immunology of transplantation, techniques and complications of dialysis, haemoperfusion and diafiltration, and general nephrology with particular emphasis, this year, on bone disease and hypertension. Finally, there are two round tables on special topics: gastrointestinal function in uraemia and the metabolism of drugs in renal failure. The latter gives guidance on the dosage of a wide range of drugs used in renal disease with references to other material and should be of interest to urologists.

Since the first volume appeared in 1964 the EDTA Proceedings has doubled its length, halved its production time and improved its format beyond recognition. The cost has increased, of course, but at 3p a page it is still very good value and deserves a place in every renal library

D N. S. K.

Book Received

BEELEY, L.: **Safer Prescribing: a Guide to Some Problems in the Use of Drugs.** Blackwell Scientific Publications, 1976. £0·90.

Conferences and Courses

SYMPOSIUM ON CLINICAL APPLICATION OF CARCINO-EMBRYONIC ANTIGEN AND OTHER ANTIGENIC MARKER ASSAYS

7th, 8th and 9th October 1977

Sponsored by the European Organisation for Research on Treatment of Cancer.

Organised by the Centre Antoine Lacassagne, Nice.

Direct inquiries and proposals of papers to Mrs F. Fein, Secretariat Symposium "Tumour Antigens", 36 Voie Romaine, 06054 Nice, Cedex, France. Tel.: (93) 80.54.23 Ext: 248. Telex: CAL NICE 470 344 F.

THE FIRST BIENNIAL LEADBETTER SYMPOSIUM ON *UROLOGIC ONCOLOGY*

For Specialists with Interest in Urologic Cancer

8th to 10th September 1977, University of Minnesota

A systematic review of urologic oncology including recent advances in relevant basic science.

For Registration Information Contact: Leadbetter Symposium, c/o Continuing Medical Education, Box 293 Mayo, University of Minnesota, Medical School, Minneapolis, MN 55455.

4th WORLD SYMPOSIUM IN PAEDIATRIC SURGERY, BARCELONA, SPAIN, JULY 1977

International Course in Paediatric Urology from 24th to 27th July 1977

Organising Chairman: Dr Rafael Gosalbez-Jorda

This international course will cover various aspects of Paediatric Urology. The following guest professors have agreed to take part: H. Hendron, P. Kelalis, J. R. King, A. Tanagho (USA), J. Cendron, J. Cuckier, J. Brueziere (Paris, France), S. J. Cohen (Manchester, England), Sami Arap (Brazil), G. Grotte (Sweden), M. Bettex (Switzerland), J. M. Gil-Vernet Vila, I Perez Bustamante, A. Puigvert, X. Sole Balcells, R. Valdes (Spain).

Applications to attend the International Course in Paediatric Urology should be sent to: Dr R. Gosalbez, c/o IV World Symposium in Paediatric Surgery, Clinica Infantil, De La Seguridad, Social, P° Valle Hebron s/n, Barcelona-16, Spain.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The List of Current Urological Literature is now arranged to correspond to the order in which papers are published in the *Journal i.e.* in anatomical order beginning with papers on the kidney.

A general selection is included at the end.

KIDNEY

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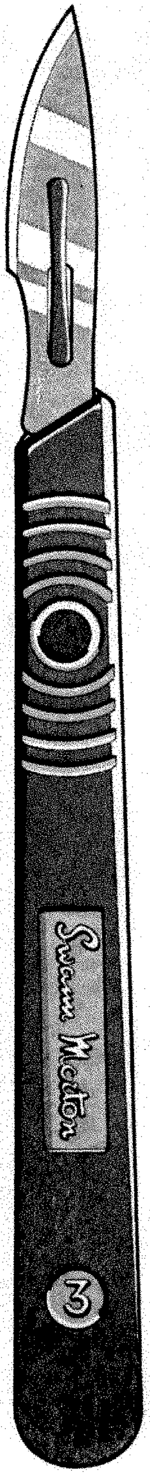

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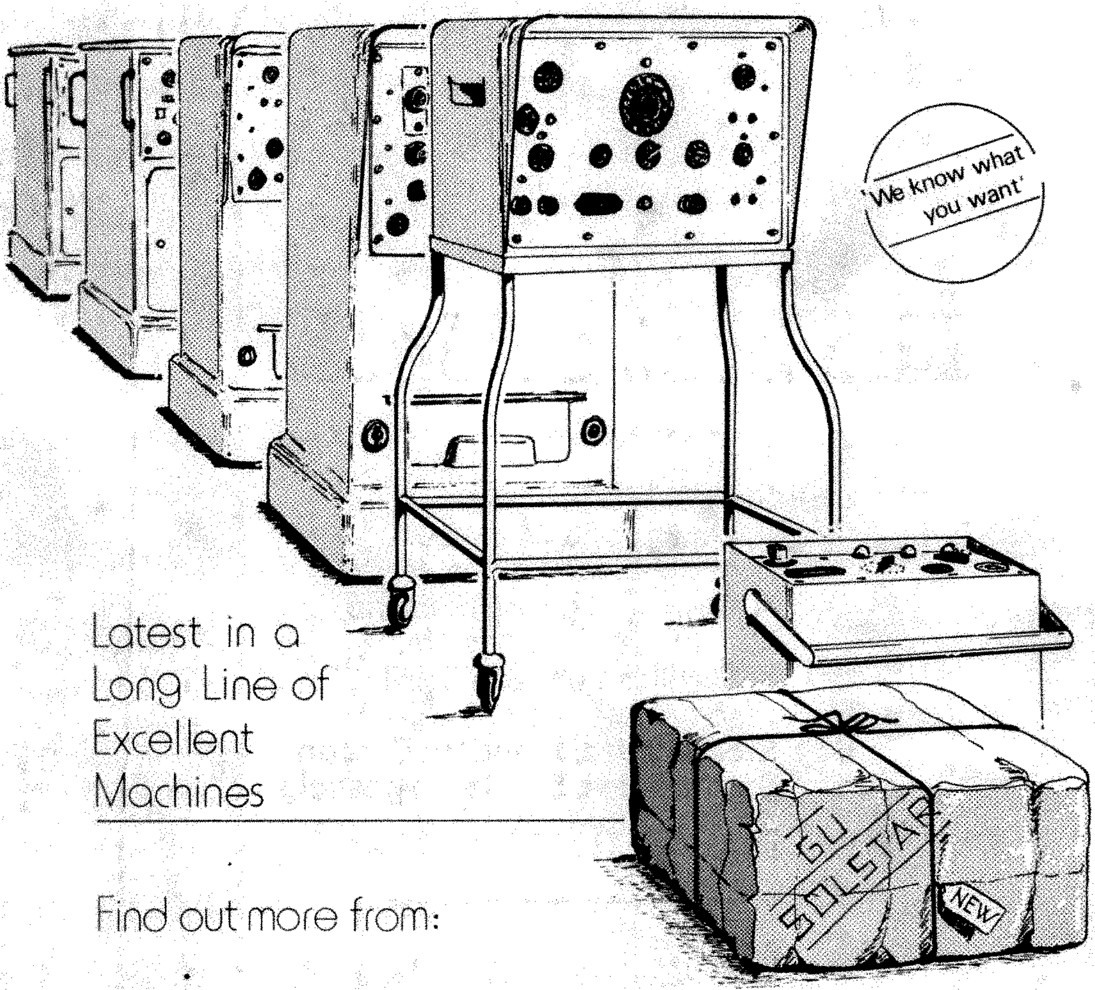
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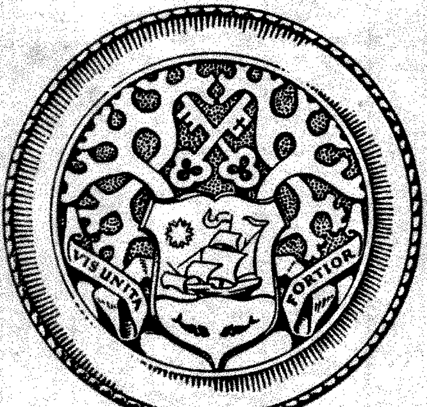

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15 Ferguson, I.R., Communication to Third Joint US/Scottish Conference on Infectious Disease, Sterling, Scotland Sept 2-4, 1976 (In Press).

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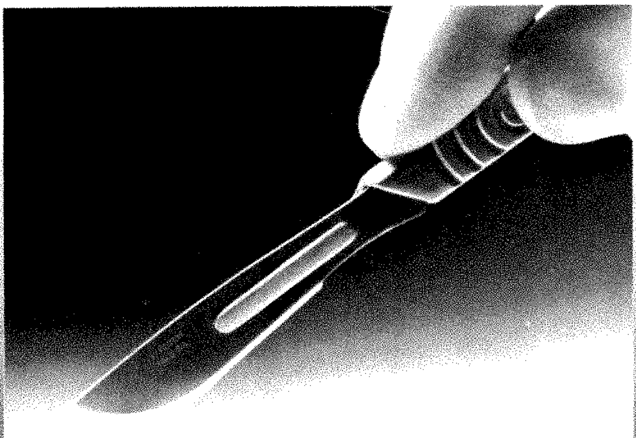

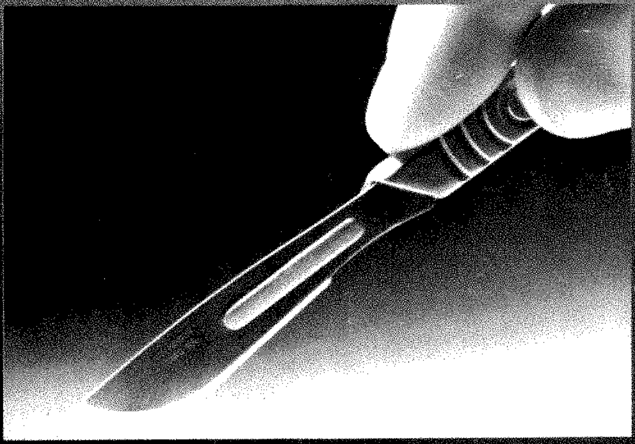

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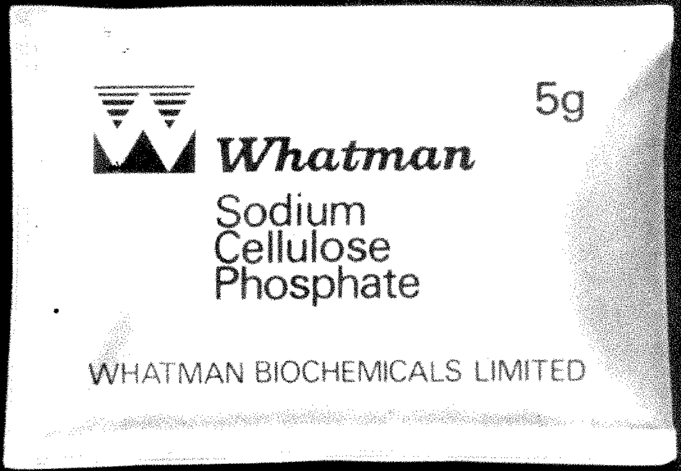

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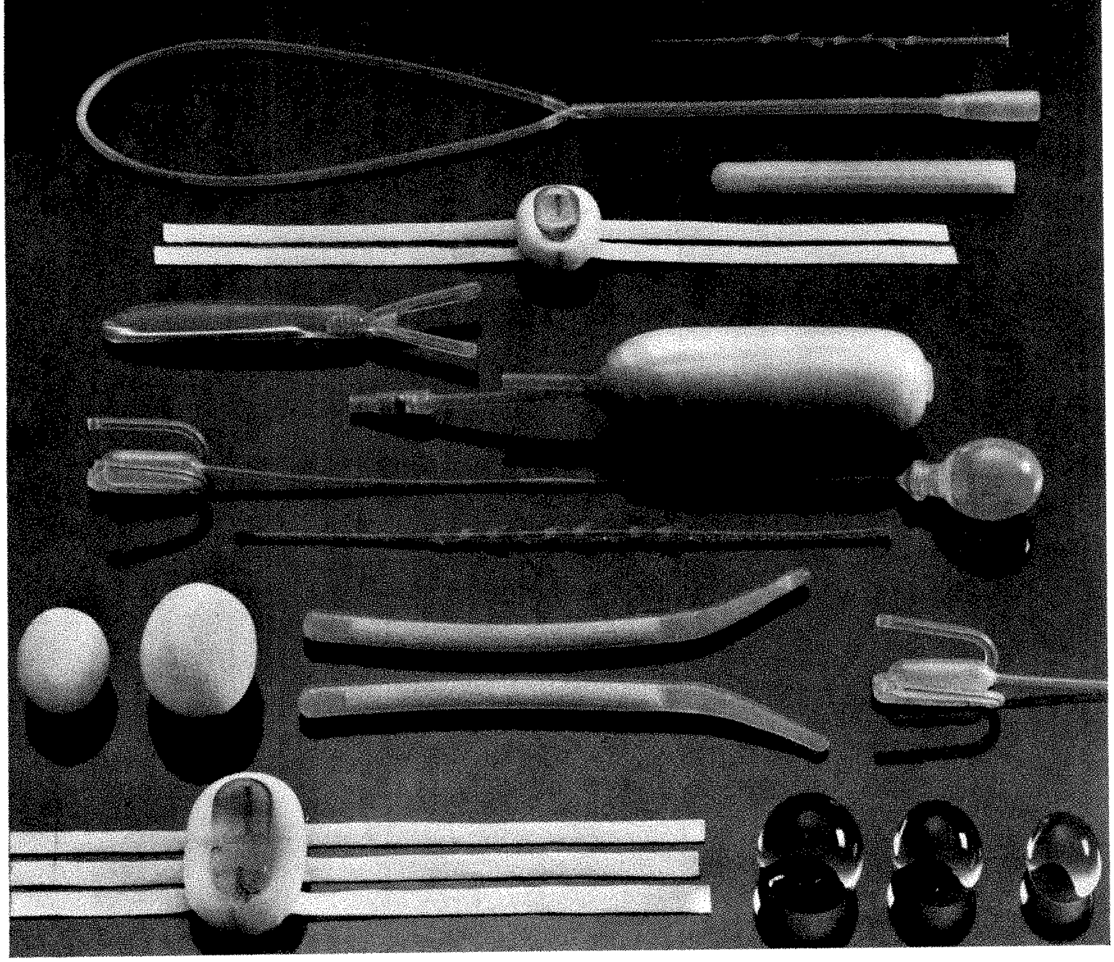

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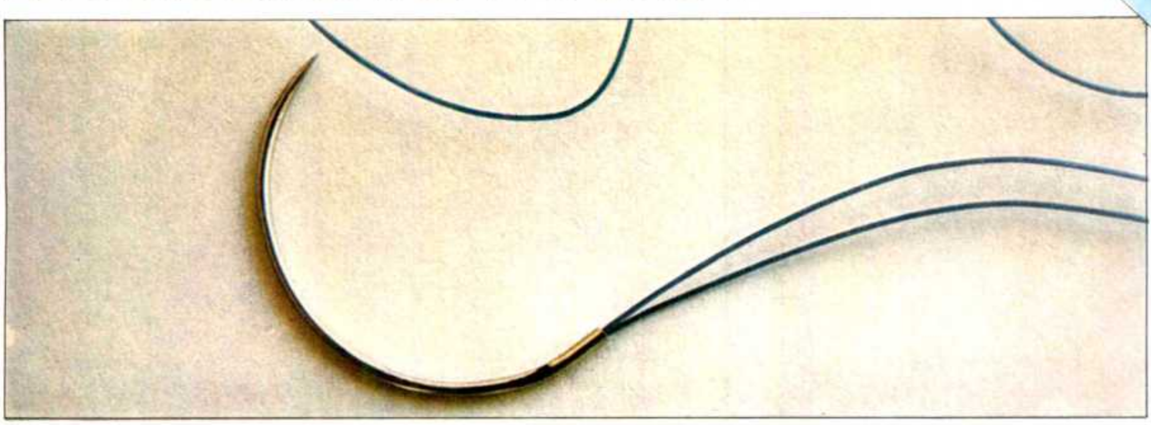

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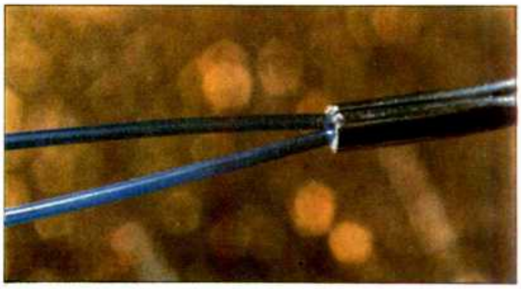

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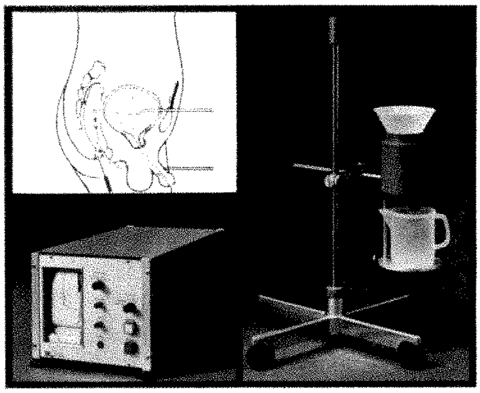

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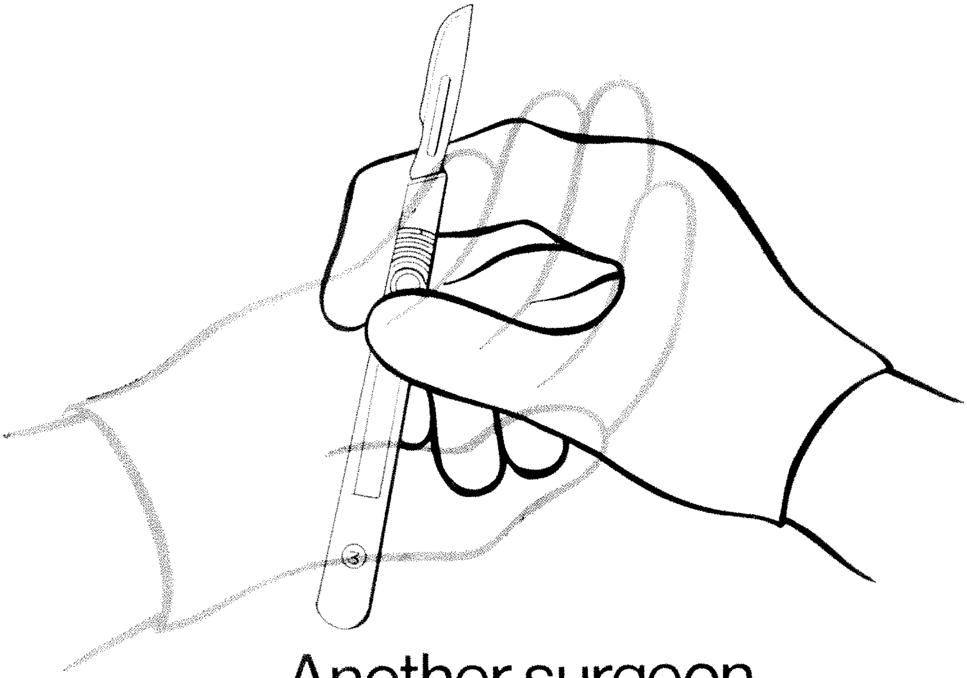

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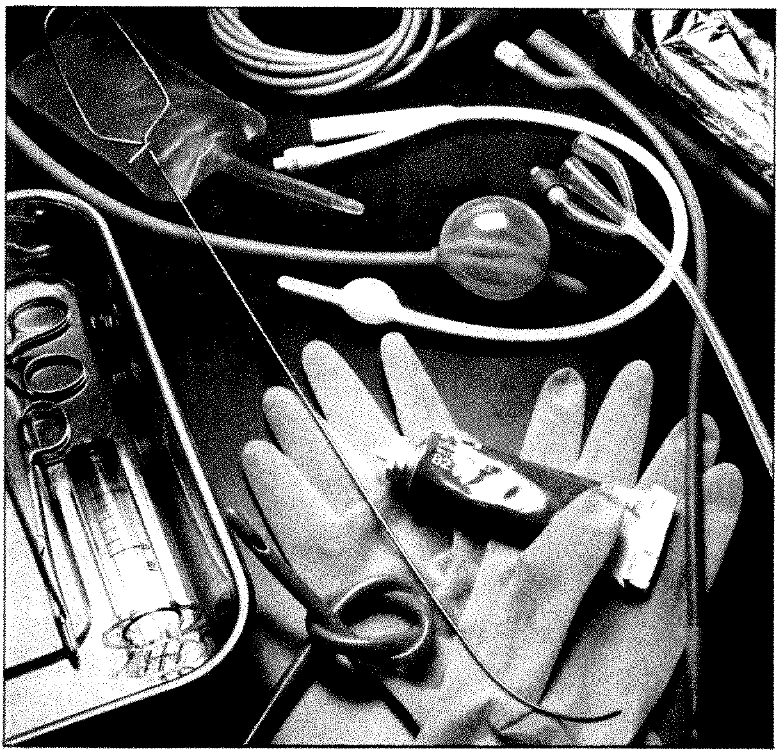

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Renal Function in Patients with Hydronephrosis

C. G. BRATT, M. AURELL and S. NILSSON

Departments of Urology and Nephrology, University of Goteborg, and Sahlgren's Hospital, Göteborg, Sweden

(Received 23 August 1976; accepted for publication 22 November 1976)

The aetiology of hydronephrosis from obstruction at the pelvi-ureteric junction is largely unknown. Several hypotheses have been put forward to explain this disease. Special emphasis has been placed on anomalies of the muscular layer in the pelvi-ureteric junction as demonstrated by Murnaghan (1957). Experimental support for local functional stenosis has been found by Bäcklund, Grotte and Reuterskiöld (1965). Operative methods for treating this type of hydronephrosis have therefore been directed towards reconstruction of the pelvi-ureteric junction. These procedures aim to improve the drainage of the renal pelvis, and so maintain or improve the renal function of the hydronephrotic side. Few reports have been published demonstrating improvement of renal function in adult patients following pyeloplasty, however, as most studies deal with the effect on the drainage of the renal pelvis only. To our knowledge there are no reports on the follow-up of cases treated conservatively. This investigation deals with the function of the renal parenchyma and the drainage of the renal pelvis in patients managed with or without operation for periods from 2-5 years.

Patients

The study comprises 50 consecutive patients with hydronephrosis due to functional obstruction at the pelvi-ureteric junction admitted to the Department of Urology during the years 1970-73.

The symptoms initiating the investigations were infection (8 patients), haematuria (16 patients), and lumbar pain (29 patients). Five patients had concomitant renal calculi. All patients were reinvestigated in 1975 at a mean observation time of 3 years (range 2-5 years). 28 patients (mean age 38 years) had been operated upon by the Anderson-Hynes' method (1949) and 10 patients (mean age 50 years) had had a nephrectomy. 12 patients (mean age 48 years) were not operated upon, mainly because of mildness of symptoms.

Investigations

In addition to routine blood and urine analyses, glomerular filtration rate measurements, isotope renography, intravenous pyelography and renal angiograms were performed in all patients. At the follow-up these investigations, except the renal angiogram, were repeated. Throughout the study repeated cultures of the urine were performed, the criteria for significant bacteriuria being those suggested by Kass (1957). In general, patients with more than 100,000 bacteria/ml urine in 2 consecutive samples were regarded as having true bacteriuria.

Methods

The following special investigations were performed.

Glomerular Filtration Rate (*GFR*). The total renal function was measured using standard clearance techniques for inulin and PAH and/or the single injection technique for GFR measurement using ^{51}Cr-EDTA-complex (Bröchner-Mortensen, 1972).

Isotope Renography. The renal *parenchymal* function of each kidney was estimated from the uptake ratio given by readings of the isotope renography curve during the first 2 min of recording. Based

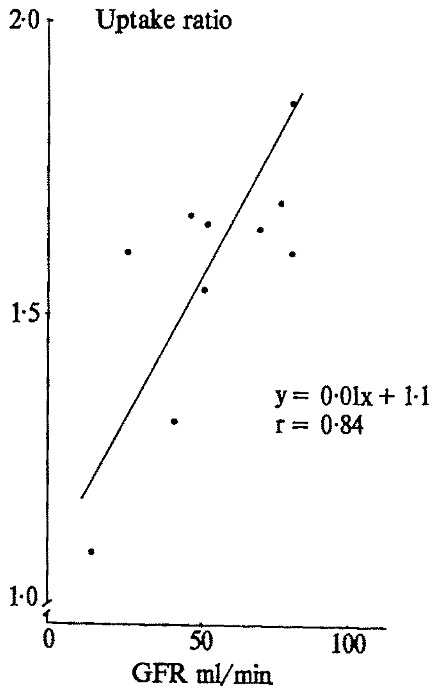


Fig. 1. Correlation in 5 patients investigated with both separate inulin clearance and renography.

on data previously published by Aurell, Jonsson and Nilsson (1971), the following criteria were applied: normal function—ratio >1·4; moderately decreased function—ratio 1·2-1·4; severely decreased function—ratio 1·0-1·2; no function—ratio <1·0. Correlation between the uptake ratio and inulin clearance has previously been established and was confirmed in our 5 patients studied with both renography and divided renal clearance, as demonstrated in Figure 1.

The isotope renogram is regarded as a sensitive test for the *drainage* function of the renal pelvis also. This aspect of the renogram has been stressed by Bergström (1971) who considered the time until the peak to be a useful index for the emptying of the pelvis. The ratio between the values for the 2 sides has been used in this investigation as an index of the relative drainage function of the hydronephrotic kidney. The following criteria were applied: normal—ratio <1·5; moderately decreased—ratio 1·5-2·0, and severely decreased—ratio >2·0.

Results

Total Renal Function

The mean preoperative glomerular filtration rate (GFR) was 96 ± 10 ml per min and the mean postoperative GFR 93 ± 8 ml per min, the difference not being statistically significant. Thus, no change in total renal function was observed in the patients who underwent surgery.

Mean GFR in the group not operated upon was 93 ± 16 ml per min at the initial investigation and 90 ± 14 ml per min at the follow-up, the difference not being statistically significant. In this group, too, the total renal function remained unchanged during the observation period of 3-5 years.

No difference was observed in serum creatinine estimated pre- and postoperatively in patients subjected to nephrectomy. In this group no change in the total renal function was found, which obviously reflects the greatly impaired function of the removed kidney.

Divided Renal Function

A. *Parenchymal Function.* Assessed by isotope renography, the preoperative parenchymal function was normal in 16, moderately decreased in 7, and severely decreased in 5 of the 28 hydronephrotic kidneys (Table I). Postoperatively the function remained normal in 16, and became normal in 6 of 7 kidneys with moderately decreased function preoperatively. 1 kidney with moderately decreased function deteriorated to severely decreased function and 1 kidney with severely decreased function showed no function at the follow-up. Thus, the renal function improved after operation in 6 (50%) of the subjects with initially reduced function and deteriorated in 2 kidneys. Both of these latter patients had undergone reoperation because of urinary leakage. In addition, 4 kidneys with severely decreased function were unchanged after the operation.

11 of the 12 non-operated patients had normal parenchymal function initially on the hydronephrotic side and 1 patient had moderately decreased function. At the follow-up, after 36 months, this kidney had severely decreased function (Table II).

As summarised in Table III, 16 of 28 kidneys in the operated group and 11 of 12 in the non-operated group had normal function initially. Postoperatively, 20 kidneys had unchanged parenchymal function, while 6 improved and 2 deteriorated. In the non-operated group of 12 kidneys 1 deteriorated during the observation period.

Table I

Renographic Classification of Pre- and Postoperative Renal Parenchymal Function in 28 Patients with Hydronephrosis

Parenchymal function	Preoperatively		Postoperatively
Normal	16		22
Moderately decreased	7	6	0
Severely decreased	5	1	5
No function	0	1	1

Table II

Renographic Classification of Renal Parenchymal Function in 12 Non-operated Patients with Hydronephrosis

Parenchymal function	First investigation		Follow-up
Normal	11		11
Moderately decreased	1	1	0
Severely decreased			1

Table III

Renographic Functional Evaluation of 28 Operated and 12 Non-operated Patients with Hydronephrosis

		Deteriorated	Unchanged	Improved
Parenchymal function	Operated	2	20 (16)	6
	Non-operated	1*	11 (11)	–
Drainage function	Operated	1	13	14
	Non-operated	3	9	–

Figures within brackets indicate kidneys with normal preoperative parenchymal function.

* 36 months of follow-up.

B. *Drainage Function.* From Table IV it will be seen that the drainage function of the renal pelvis assessed by isotope renography was preoperatively within normal limits in 3 kidneys, moderately decreased in 4, and severely decreased in 21. Postoperatively, normal drainage was observed in 6 kidneys, 3 of which were normal preoperatively. Of 4 kidneys with moderately decreased drainage function preoperatively, 2 were unchanged, 1 improved and 1 deteriorated. Of 21 kidneys with severely decreased function preoperatively, the drainage was normal in 2, improved in 11 and unchanged in 8.

Table V shows that in the non-operated group of 12 kidneys the drainage function was initially normal in 1, moderately decreased in 4 and severely decreased in 7. At the follow-up no kidney had normal drainage function. 2 kidneys with moderately reduced drainage function initially had deteriorated to severely decreased function.

To summarise (Table III), the drainage function improved on operation in 14 kidneys, remained unchanged in 13 and deteriorated in 1. In the non-operated group the drainage function remained unchanged in 9 and deteriorated in 3 kidneys.

Other Observations. Significant bacteriuria was observed preoperatively in 8 out of 21 patients. At the postoperative investigation positive urine cultures were obtained in 3 patients. Among the 12 patients not operated upon, 4 had bacteriuria at the first investigation compared to none at the follow-up.

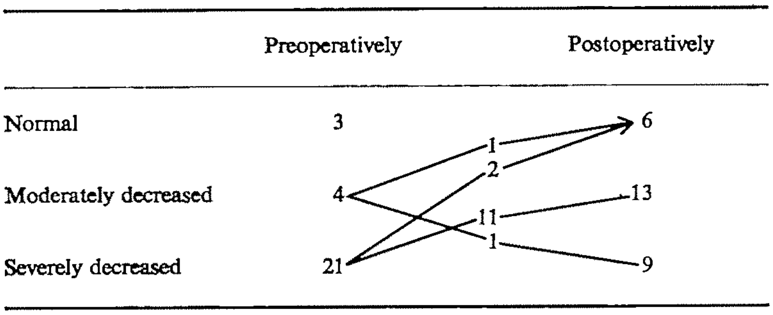
No calculi were observed in the operated group at the follow-up. 2 patients in the non-operated group developed calculi in the hydronephrotic kidney during the observation period. They had no symptoms other than microscopic haematuria.

Discussion

Determination of the function of the hydronephrotic kidney presents several problems. The classical clearance technique applied as a divided kidney function test is time-consuming and may cause pain, bleeding and infection. Also, in urological studies the results of this technique are reliable in only 50% and acceptable in another 25% (Fritjofsson and Aurell, 1968). The determination of renal parenchymal function using isotope renography therefore offers definite advantages. Aurell, Nilsson and Jonsson (1971) demonstrated good correlation between the uptake ratio calculated within the first 2 min of the renographic registration and the clearance value of individual kidneys. Their results are further verified by the fairly good correlation in 5 patients investigated with both techniques in the present study. Isotope renography has also been shown to be a useful method for evaluation of the drainage function of the renal pelvis.

Table IV

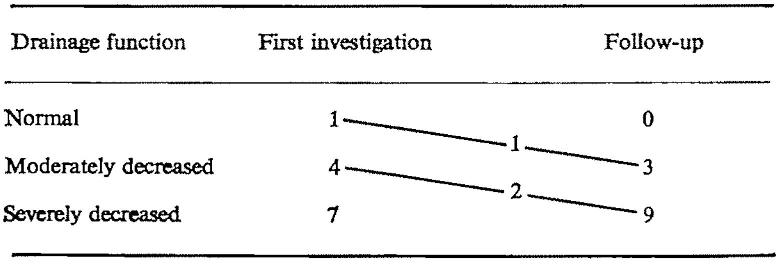
Renographic Classification of the Pre- and Postoperative Drainage Function of the Renal Pelvis in 28 Patients with Hydronephrosis



	Preoperatively		Postoperatively
Normal	3		6
		1	
		2	
Moderately decreased	4		13
		11	
		1	
Severely decreased	21		9

Table V

Renographic Classification of Drainage Function of the Renal Pelvis in 12 Non-operated Patients with Hydronephrosis



Drainage function	First investigation		Follow-up
Normal	1		0
		1	
Moderately decreased	4		3
		2	
Severely decreased	7		9

In fact, when isotope renography was introduced in clinical medicine in 1956 it was the possibility the technique provided of evaluating the urinary excretion from the pelvis which was especially appreciated. This function has been especially studied by Bergström (1971) in obstetric patients. In experimental studies he demonstrated that the delay in time until the peak of the renogram might result from either a raised pelvic volume or a low urinary flow rate. The time until the peak of the renogram is mainly determined by the ratio of the pelvic volume to the urine flow rate. Under standardised conditions of hydration the isotope renogram was found to be a convenient method of assessing the drainage function.

Surgical correction of pelvic-ureteric obstruction is generally considered to be a rather urgent procedure due to the threat to renal function. Our study demonstrates, however, that in adults there is usually no demonstrable reduction of the renal parenchymal function on either side. Furthermore, in cases not operated upon no major reduction in parenchymal function was found during 3-5 years of observation. Obviously, in hydronephrotic kidneys without reduced function the indication for surgery must be based on factors other than maintenance of renal function. In patients with uncomplicated pelvi-ureteric obstruction and no decrease in renal function a conservative approach is therefore strongly recommended. Adoption of a conservative approach in these cases is also supported by our experience that if complications occur reoperation is not likely to give optimal results.

We have followed patients with hydronephrosis not operated upon for 3-5 years. In this group only 1 patient had deteriorating renal parenchymal function. This was a 65-year-old woman with chronic pyelonephritis and slight hypertension. The deterioration of the renal function might therefore not have been due to hydronephrosis in this patient.

Postoperatively, 14 of 28 patients in our study exhibited improved drainage function. This is a rather low figure but corresponds well with the data presented by Davies, Jones and Croft (1969) who demonstrated an improvement in pelvic emptying in 10 out of 20 operated kidneys. The improvement rate varies considerably in different studies however. Tveter, Nerdrum and Mjølnerød (1975) recently observed a "cure" rate of about 75% 3 months after operation and almost 100% after 1 year, while Otnäs, Rothwelt and Mathiesen (1975) found an improvement in about 30% of patients after an average follow-up of 24 months. The reason for the varying results in different clinical series is not immediately apparent but may well be related to differences in patient materials and methods of operation.

The drainage function in the non-operated series deteriorated in 3 kidneys. None of these 3 patients had pain or infection during the observation period, but 2 of them developed calculi in the hydronephrotic kidney and had haematuria. Consequently, 2 out of 12 patients in our control group had to be operated upon at the end of the follow-up.

Isotope renography is perhaps not the most suitable method for evaluation of improvement of drainage function after operation for hydronephrosis. It is well known that although the operation may be considered successful the pelvi-calyceal system, which has been dilated for a long period of time, rarely returns to normal and the remaining pelvis may thus be rather capacious. After surgical correction of the pelvi-ureteric junction the excreted isotopes may in such cases remain in the pelvi-calyceal system for quite a long time despite the improved drainage, and the renogram curve will still not show signs of delayed emptying.

In conclusion, our results clearly indicate that the renal parenchymal function is not decreased in the majority of patients with hydronephrosis secondary to pelvi-ureteric obstruction. The indication for operation in these patients must therefore be based on factors other than the possible threat to the renal function. The indications would thus include pain, haematuria, and infection. During our follow-up of non-operated patients the formation of calculi occurred in 2 patients but no major decrease in renal function was found. A conservative approach to surgery in uncomplicated hydronephrosis with intact renal function seems to be warranted particularly because of the difficulties in preserving renal function after surgical complications which might necessitate nephrectomy.

Conservative treatment of hydronephrosis is, however, recommended only if adequate yearly control examinations can be arranged. The schedule should include an assessment of the total renal function by clearance measurements, divided renal function by isotope renography and plain films of the upper urinary tract for the detection of renal calculi.

Summary

The glomerular filtration rate and pelvic drainage function were reinvestigated after 3-5 years in 50 patients with hydronephrosis secondary to functional obstruction in the pelvi-ureteric junction.

Pyeloplasty by the Anderson-Hynes' technique had been performed in 28 kidneys, while 12 patients were not operated upon and 10 had had a nephrectomy.

The glomerular filtration rate was determined with the clearance technique and isotope renography.

16 out of 28 kidneys subjected to pyeloplasty and 11/12 non-operated kidneys had a normal renal parenchymal function at the first investigation in spite of severely disturbed drainage function. In the non-operated series the renal parenchymal function was unchanged in 11 patients. Deterioration was observed in 1 kidney, probably because of chronic pyelonephritis.

Uncomplicated cases of pelvi-ureteric junction obstruction should not be operated upon unless necessitated by symptoms.

A yearly control programme including a renal function test and plain films of the upper urinary tract is recommended for these patients.

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The Authors

C. G. Bratt, MD, Senior Registrar.
M. Aurell, MD, Assistant Professor of Nephrology.
S. Nilsson, MD, Associate Professor of Urology and Head of Department.

Requests for reprints: S. Nilsson, Department of Urology, Sahlgren's Hospital, 413 45 Göteborg, Sweden.

British Journal of Urology (1977), 49, 256 ©

Short Case Report

Localisation of Adrenal Adenoma with I 131-19 Iodocholesterol

A 34-year-old woman had all the clinical findings typical of patients with Cushing's syndrome. Diagnosis was confirmed by hormonal investigations which showed, chiefly, elevated cortisol levels in blood and urine.

Localisation of the lesion was attempted with various radiological examinations, such as retroperitoneal pneumography combined with IVP and tomography scanning of the kidneys and selective arteriography of the adrenals. However, localisation of the lesion was not possible.

Only visualisation of the adrenal glands, following the administration of a dose of I 131-19 iodocholesterol, permitted us to determine the existence of a small adenoma in the left adrenal (Fig.).

The subsequent operation, for the removal of the adenoma of the (L) adrenal, confirmed the preoperative diagnosis based on scintigraphic findings of the adrenals.

Postoperatively, there was a progressive improvement in clinical and laboratory findings.

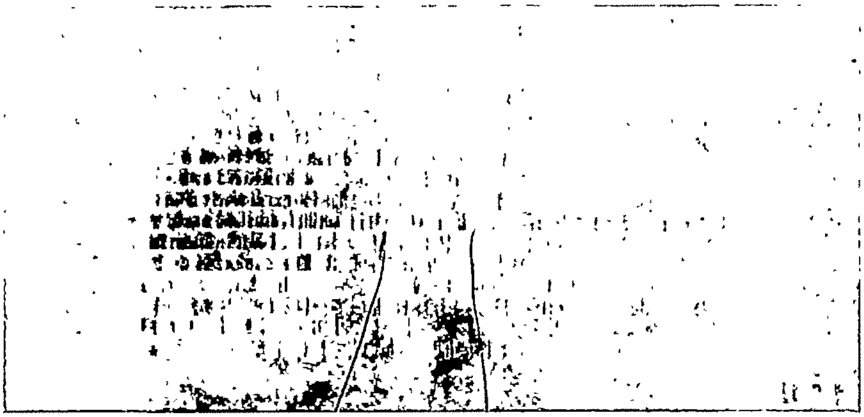

Fig. (Left and right.) Scanning of the adrenal glands with I 131-19 iodocholesterol on the 11th day. Note the clear appearance of the adenoma on the left.

Comment

Visualisation of adrenal glands with I 131-19 iodocholesterol proposed by Beierwalters *et al.* (1971) is a safe (Ansari *et al.*, 1972), simple and valuable procedure independently showing the localisation and nature of the lesion.

C. Dimopoulos and D. Ikkos
Department of Urology, General State Hospital of Athens; Department of Endocrinology and Radio-isotope of the Hospital Evangelismos, Athens

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Causes of Renal Deterioration in Patients with Meningomyelocoeles

K. LIGHT and P. J. P. VAN BLERK

Division of Urology, University of the Witwatersrand Medical School, and The Transvaal Memorial Hospital for Children, Johannesburg

(Received 17 January 1977; accepted for publication 15 February 1977)

The neonatal mortality in patients born with meningomyelocoeles has decreased markedly due to aggressive surgical treatment (Eckstein and Macnab, 1966). If a child survives infancy, the natural renal history is one of progressive deterioration (Mebust, Foret and Valk, 1969; Smith, 1972a). The rate of deterioration varies markedly in individual patients and a child must therefore be under constant surveillance as this may be silent. The aim of this study was to define the causes of upper tract deterioration which would then allow for more effective management.

Methods and Materials

The patient records of 122 children attending the Spinal Defects Clinic at the Transvaal Memorial Hospital were analysed (Table I). The follow-up period was from 2 to 10 years. Initially all patients were managed with the Credé manoeuvre for bladder emptying but this was found to be totally inadequate in controlling the urological problems. More recently, clean intermittent catheterisation has been introduced as an alternative, the results of which will be fully reported later. During earlier years, urological assessment consisted of annual intravenous pyelogram (IVP) and 3-monthly urinalysis and culture. Renal function studies were only performed prior to any major surgery and 2 voiding cysto-urethrogram (VCU) only if the IVP was abnormal. More recently, urological evaluation has included routine annual IVP and VCU and 3-monthly urinalysis and culture as well as a urodynamic evaluation in selected cases. Ureteric abnormalities were defined as dilatation, obstruction and reflux. Reflux was graded as follows: grade I, reflux into lower half of ureter only; grade II, into the renal pelvis with no significant dilatation; and grade III, into the renal pelvis with significant dilatation. A random group of 26 patients with upper tract damage was analysed to establish the presence of a possible common factor. Renal damage was graded into: scarring and clubbing only, significant hydronephrosis and retarded renal growth.

Results

Neonates

A total of 52 patients had an IVP alone (Table II). Of these only 2 (3.8%) showed upper tract abnormalities. 34 of the above patients had a VCU as well which revealed 10 upper tract abnormalities, 9 with reflux and 1 with mild

Table I

Material

Age sampling from total of 122 patients	
Neonatal	52
2 years	51
4 years	33

Table II

Neonatal

	Patients (No.)	Normal	Abnormal	% Abnormal
IVP	52	50	2	3·8
IVP+VCU	34	24	10	19·4

Table III

Neonatal Abnormals

Total	Reflux I	II	III	Dilatation	Obstruction
10	2	3	4	1	–
% of 34 pts	5·8	8·8	11·8	2·9	0

Table IV

2 Years

	Total	Normal	Abnormal	% Abnormal
IVP	51	35	16	31·4
IVP+VCU	37	18	19	51·3

Table V

2 Year Abnormals

Total	Reflux I	II	III	Dilatation	Obstruction
19	4	3	8	3	1
% of 37 pts	10·8	8·1	21·6	8·1	2·7

Table VI

4 Years

	Total	Normal	Abnormal	% Abnormal
IVP	33	26	7	21·2
IVP+VCU	27	21	7	25·9

Table VII

4 Year Abnormals

Total	Reflux I	II	III	Dilatation only	Obstruction
7	2	1	2	1	1
% of 27 pts	7·4	3·7	7·4	3·7	3·7

hydronephrosis not associated with reflux or obstruction. Therefore, the incidence of upper tract abnormalities using both modalities was 29·4%. The 10 abnormal cases were analysed further (Table III) and it was found that grade III reflux was present in 4 (11·8%). As only 1 of these 4 cases had upper tract dilatation on IVP, it follows that significant reflux may initially be present with apparently normal upper tracts.

2 Years

51 patients had an IVP as the only radiological investigation (Table IV), 16 (31·4%) had upper tract abnormalities. A VCU was performed in addition in 37 of the above patients and 15 with reflux were found. 19 patients had abnormal upper tracts using both modalities, an incidence of 51·3%. On further analysis (Table V), grade III reflux was found to be present in 8 (21·6%) and obstructive hydroureter in 1 (2·7%). The incidence of lesser degrees of reflux and ureteric dilatation is also shown.

4 Years

33 patients had an IVP alone (Table VI) with 7 (21·2%) having upper tract abnormalities. 27 of the above patients had a VCU in addition and 5 cases with reflux were found. 7 (25·9%) were found to have upper tract abnormalities with IVP and VCU. A further analysis of these 7 cases is shown in Table VII, where grade III reflux occurred in 7·4% and obstruction in 3·7%.

Random Group

26 patients had radiological evidence of upper tract deterioration. This involved 38 renal units. All patients had an IVP and VCU (Table VIII). The degree of deterioration was graded into scarring and clubbing (10 units), significant hydronephrosis (22 units), and retarded renal growth (6 units). In looking for a common factor it was seen that grade III reflux was present in 63·2% while obstructive hydroureter was present in 15·8%. On grouping the severe upper tract changes together, *i.e.* hydronephrosis and retarded renal growth, grade III reflux was present in 71·4% and obstructive hydroureter in 21·4%. These latter 2 conditions accounted for 92·8% of the severe upper tract damage.

Discussion

The results obtained show that at birth 11·8% of patients had significant reflux. All these had developed significant renal damage by the age of 2 years. The total incidence of upper tract change at 2 years was 51·3%. Not all these patients are at risk, however, as the incidence of severe upper tract damage at 2 years was 23·5%. At 4 years this figure was 18·5%. Therefore, by the age of 4 years, 42% of patients had significant upper tract changes which is similar to the figure of 40% quoted by Smith (1972). 76·9% of our medically indicated diversions were performed within the first 4 years of life.

Urinary infection in these patients has been incriminated as playing an important role in upper tract deterioration (Cooper, 1967; Cass, 1976). We have previously reported that the role of bacteriuria is inconclusive, as in our experience, the incidence of sterile urine in patients with abdominal upper tracts was 42·9% (Light and van Blerk, 1976). Infection in the presence of obstruction will, however, cause rapid destruction of renal tissue.

Table VIII

Random Group of Abnormals

		Reflux					
	Renal units	I	II	III	Obstruction	Normal	Dilatation
Scarring and/or clubbing	10	3	1	4	–	1	1
*Hydronephronis	22	–	1	16	5	–	–
*Retarded renal growth	6	–	–	4	1	–	1
Total	38	3	2	24	6	1	2
%		7·9	5·3	63·2	15·8	2·6	5·3
*Hydro.+RRG %		0	3·6	71·4	21·4	0	3·6

The results in the random group clearly show that grade III reflux followed by obstructive hydroureter are by far the most common factors associated with upper tract deterioration. There is no doubt that grade III reflux, whether congenital or acquired is the most important precursor of upper tract damage. The 11·8% incidence of grade III reflux in the neonate represents those patients risking the development of subsequent renal damage.

The greatest number of patients deteriorate within the first 2 years with another smaller peak at 4 years. Subsequently, the number of patients showing renal deterioration falls markedly although a small number will go on to develop this at sporadic intervals. At present we have 20 patients aged 10 to 15 years of whom only 6 (30%) have upper tract changes. This is at variance with the results reported by Mebust *et al.* (1969) who stated that 90% of girls and 60% of boys had deteriorated after the age of 10 years. Also, 3 of the above 6 patients have only minor renal changes such as clubbing or scarring which have remained static for the past 5 years.

Something therefore, happens early in life to account for the often rapid renal deterioration. We feel that the development of a high-pressure system within the bladder precedes the onset of grade III reflux or obstructive hydroureter in the majority of cases. This high pressure may be due to a primary upper visceromotor lesion of the bladder or secondary to a "spastic" external sphincter representing an upper somatomotor lesion. The reason why this high pressure bladder develops only after birth, usually within the first 2 years, may be because of spinal shock which disappears at various intervals following delivery. Studies are currently being undertaken to investigate this hypothesis. Patients who do not develop this high intravesical pressure are less likely to develop severe renal damage. Currently, therefore, it is our policy to perform an IVP and VCU at 6-monthly intervals until the age of 2 years in order to detect the early presence of grade III reflux or obstructive hydroureter. If either of these conditions is present, the patient is immediately started on intermittent catheterisation as a preliminary method of management.

Summary

The patient records of 122 children with meningomyelocoeles were analysed in an attempt to find a common factor causing upper tract deterioration.

The results clearly show that grade III reflux followed by obstructive hydroureter are the commonest factors associated with significant renal deterioration.

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The Authors

K. Light, FCS(SA), Consultant, Urological Surgeon and Lecturer.
P. J. P. VAN BLERK, Dip.Surg, Professor of Urology.

Requests for reprints: K. Light, Department of Urology, University of the Witwatersrand Medical School, Johannesburg, Republic of South Africa.

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Renography as a Prognostic Index of Urinary Tract Problems in Childhood

M. BROCK, R. C. L. FENELEY and E. R. DAVIES

Department of Urology and Radiodiagnosis, Bristol Royal Infirmary

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Accurate assessment of the significance of urinary tract symptoms in children is of great importance, as progressive renal damage may occur in the presence of anatomical or functional abnormalities which are amenable to surgery (Govan and Palmer, 1969; Scott, 1969) or intensive medical treatment (Blight and O'Shaughnessy, 1969), Excretion urography and micturating cysto-urethrography, are important in this assessment, but both methods have disadvantages. These include radiation dose to the gonads, especially if both tests are done (Kaude, Lorenz and Reed, 1969; Fendel, 1970), the risk of adverse reaction to intravenous contrast agents (Saxton, 1969; Davies, Roberts and Roylance, 1975), and the psychological and possible physical trauma of MCUG to the young patient (McAllister, Cacciarelli and Shackelford, 1974).

These shortcomings do not apply to renography (Shuler, Meckstroth and Maxfield, 1970), which is an atraumatic test that records renal tubular excretion of ortho-iodo-hippurate (Hippuran), its transit through the kidney and its drainage from the renal pelvis. Renography is a test of function, and does not give any anatomical or structural information about the kidneys, so that the apparent attractions of the technique are counterbalanced by its lack of specificity (Bligh, Davies and Leach, 1976). In order to determine its place in the investigation of urinary tract problems in childhood, a small group of unselected children was studied and the results were correlated with the outcome of the illness after a follow-up interval of 7 years.

Table I

Comparison of Renography and Radiography in all Patients

	Renography normal	Renography abnormal	Total
Radiography normal	25	5	30
Radiography abnormal	9	45	54
Total	34	50	84

Table II

Comparison of Renography and Radiography in 35 "At Risk" Patients

	Renography normal	Renography abnormal
Radiography normal	0	0
Radiography abnormal	0	35

Patients and Methods

91 children over the age of 2 years were studied. They were referred consecutively with urological problems to the Bristol Childrens' Hospital during a 3-month period in 1968-69.

(*a*) *Initial Assessment*

All the children presented with urinary tract symptoms. In addition to clinical assessment, all had excretion urography supplemented where necessary by micturating cysto-urethrography. All had Hippuran renography and on the evidence then available (Winter, 1966) ^{125}I was the isotope of choice. The renograms were obtained using a simple probe system without background subtraction. Because of the inherent inaccuracies of this system only the following general criteria of abnormality were used:

(*a*) Rounding of the peak of the trace.
(*b*) Failure of activity to fall by 50% within 10 min of peak.

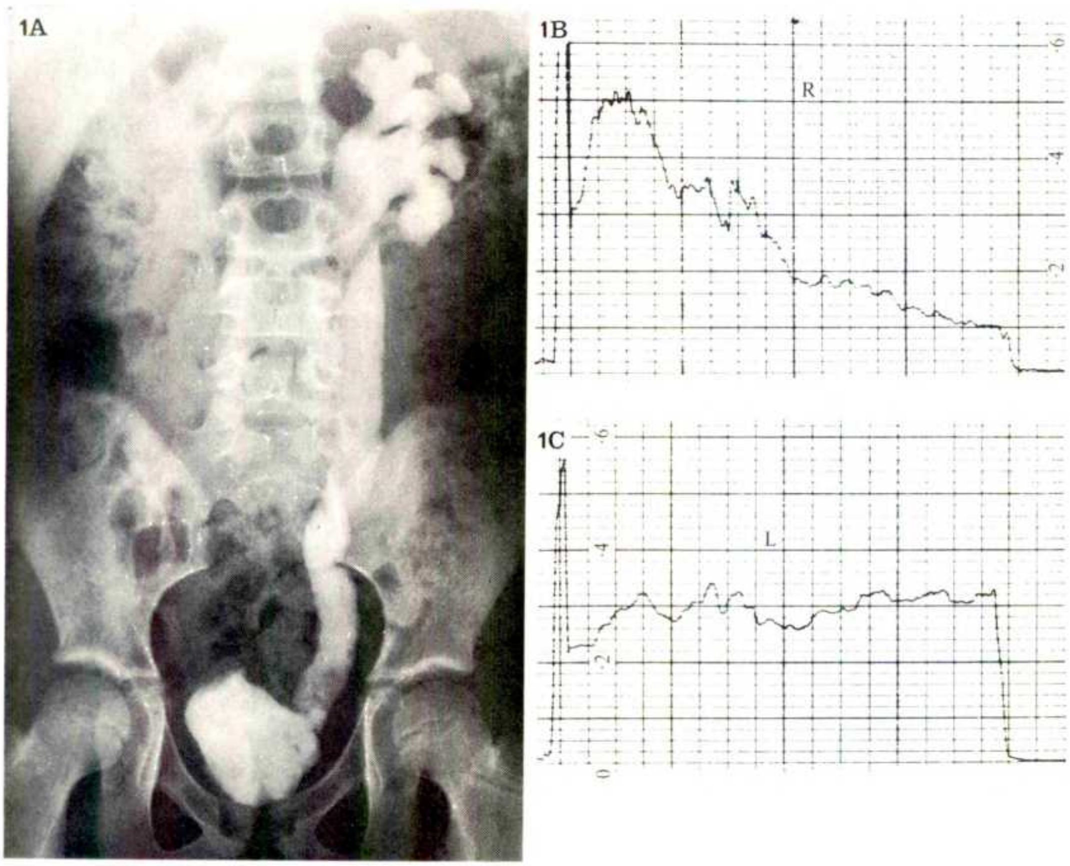

Fig. 1. T. D. Female, aged 8 years. Enuresis and frequent urinary tract infections. (a) Micturating cysto-urethrogram showing neurogenic bladder and free reflux into dilated left ureter, pelvis and calyces (Grade III); (b) ^{125}I Hippuran renogram: right trace—normal; (c) ^{125}I Hippuran renogram: left trace—low flat trace indicating impaired function and drainage.

(*c*) Transit time (from time of injection to peak of trace) more than 25% longer than other side.

(*d*) Slope of the third phase 25% less than that of contralateral trace.

Each renogram was classified as normal or abnormal without knowledge of the radiological findings.

(*b*) *7-Year Follow-up Assessment*

It was considered unethical to repeat all the radiological examinations at the time of follow-up, although some cases had had follow-up radiological examinations for clinical reasons. The 7-year assessment was clinical and based on:

(*a*) Deterioration of renal function or progression of renal damage.

(*b*) Whether an operation had been necessary on the urinary tract.

Children who were in either of these groups were identified as being "at risk" and the ability of the original investigation to predict this group was assessed.

Table III

49 Patients Not At Risk over 7-year Follow-up

	Renography normal	Renography abnormal
Radiography normal	25	5
Radiography abnormal	9	10
Total	34	15

Table IV

Abnormal Radiological Findings

		Renogram normal	Renogram abnormal	Total
Vesico-ureteric reflux	Unilateral	7	13	20
	Bilateral	2	19	21
Hydronephrosis		–	10	10
Chronic pyelonephritis		–	2	2
Ureterocoele		–	1	1
Total		9	45	54

Table V

Severity of Reflux in 63 Kidneys (41 Patients)

Severity of reflux	Renogram abnormal		Renogram normal
	Not at risk	At risk	
Grade I	3	0	3
Grade II	5	13	6
Grade III	8	21	4*
Total	16 (10 patients)	34 (22 patients)	13 (9 patients)

* Only one of these had reflux after medical treatment.

Results

7 patients were lost to follow-up and the study has been completed in 84 patients (Table I).

35 of these patients were "at risk"; 31 had surgical treatment, 2 had deterioration of renal function and 2 had progression of pyelonephritic scarring. *All* of the patients "at risk" had abnormal radiographs and renograms (Table II). An example is shown in Fig. 1.

The remaining 49 patients were not "at risk" (Table III). In 25 of these both radiographs and renograms were normal, but in 10 *both* tests were abnormal. In the other 14 either radiographs (9) or renograms (5) were abnormal.

The radiographic abnormalities are listed in Table IV. All had abnormal renograms except for 9 patients with vesico-ureteric reflux who were not "at risk" (Table III) (Fig. 2). Vesico-ureteric reflux was overall the commonest radiographic abnormality. All the patients with hydronephrosis, chronic pyelonephritis or ureterocoele had abnormal renograms and radiograms (Fig. 3),

The severity of reflux was slightly greater in patients who were "at risk" (Table V). Grade III reflux was found in 4 kidneys with normal renograms but in 3 of these it resolved after a period of medical treatment.

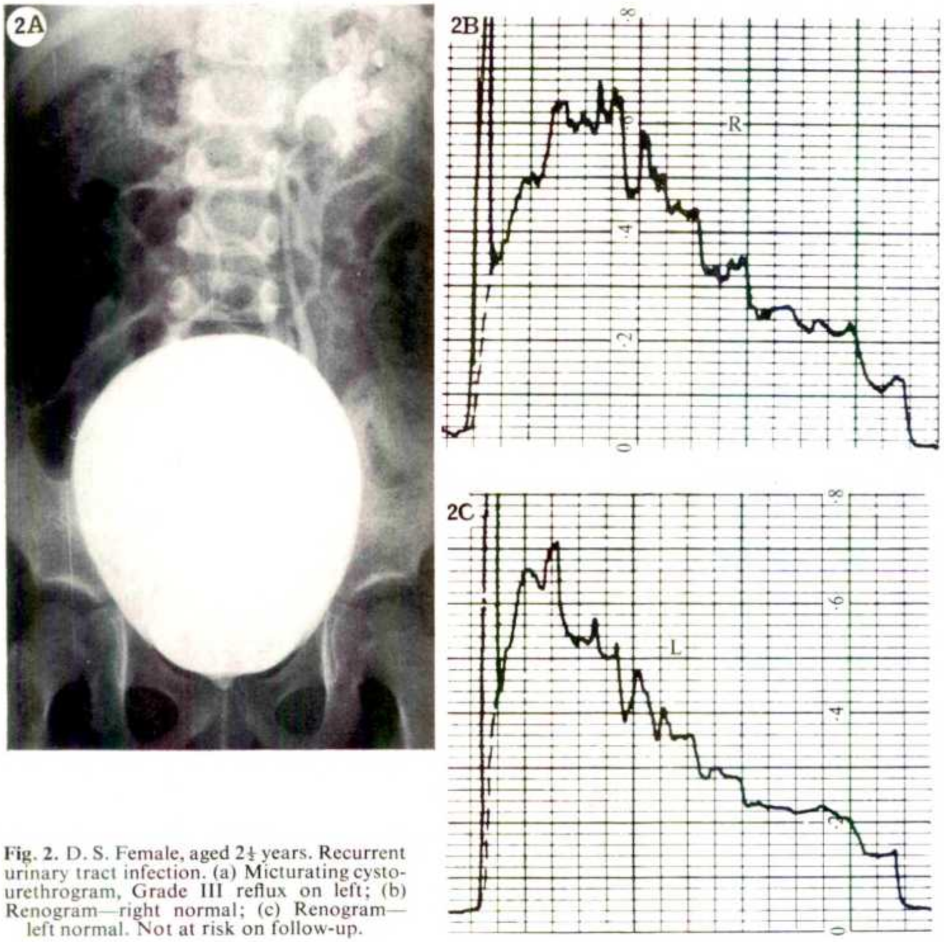

Fig. 2. D. S. Female, aged 2½ years. Recurrent urinary tract infection. (a) Micturating cystourethrogram, Grade III reflux on left; (b) Renogram—right normal; (c) Renogram—left normal. Not at risk on follow-up.

Discussion

The most important result to emerge is that when both renograms and radiograms were abnormal 80% of the patients were at risk, and all the patients at risk were in this group. The combination of tests thus identified accurately the patients needing careful surveillance. The 20% who were finally declared to be not at risk could not have been predicted from the initial tests. It is not surprising that abnormal tests were sometimes associated with a good outlook because the commonest abnormality was vesico-ureteric reflux and it is well known that reflux is often transient (Allen, 1970), particularly when treated energetically (Smellie, 1970) as in this group.

Conversely none of the patients with normal renograms was at risk. 9 of these patients are of particular interest because they had abnormal radiographs. All had vesico-ureteric reflux which would not have been discovered if renography had been used as a screening test for radiograms (Table IV). Careful examination of the records of these patients shows that the subsequent treatment was essentially symptomatic and not influenced by functional abnormality. Thus the disquiet over misleading normal renograms is offset by the fact that none of them was at risk and therefore no ultimately serious lesions were undetected. At least 2 important factors contributed to this difference. Firstly, micturating cysto-urethrography was always done supine,

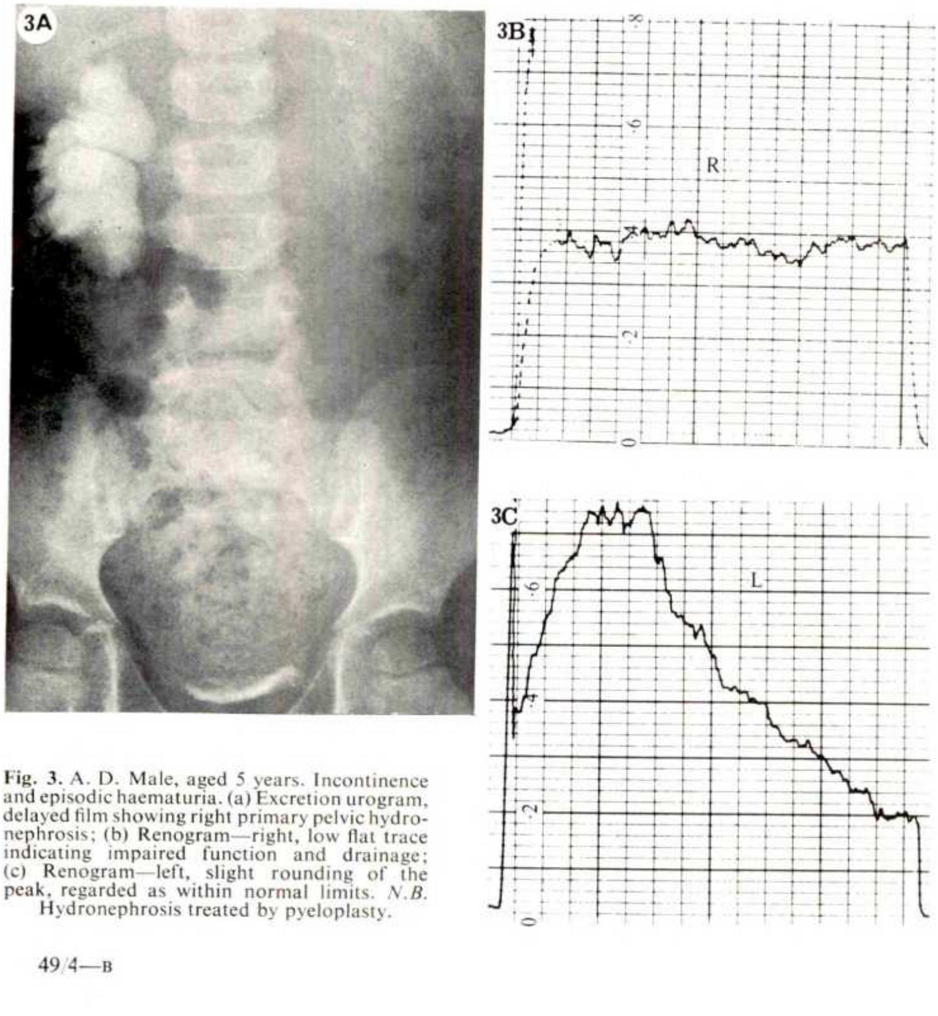

Fig. 3. A. D. Male, aged 5 years. Incontinence and episodic haematuria. (a) Excretion urogram, delayed film showing right primary pelvic hydronephrosis; (b) Renogram—right, low flat trace indicating impaired function and drainage; (c) Renogram—left, slight rounding of the peak, regarded as within normal limits. *N.B.* Hydronephrosis treated by pyeloplasty.

whereas renography was always done erect, so that the renogram could be normal unless micturition took place during the test. Secondly reflux into the renal pelvis is less important than intrarenal reflux, which is associated with renal damage (Rolleston, Maling and Hodson, 1974). It is suggested that renography was normal when the less severe type of reflux was present and that abnormal renograms occurred only with the more serious intrarenal reflux. It requires a meticulous technique to show intrarenal reflux at micturating cysto-urethrography and it has not been shown in children over the age of 6 years (Maling and Rolleston, 1975). It is suggested that standard renography is a sensitive indicator of the potential seriousness of such reflux when it occurs. Its conversion to normal may well be useful in assessing the effectiveness of treatment.

In contrast are the 5 patients whose renograms were abnormal despite normal radiograms. The probable explanation of this paradox is the non-specific nature of the renogram. In addition to being affected by impaired parenchymal function and impaired ureteric drainage it is influenced by low urine flow rate (*e.g.* in dehydration) (Wenzl *et al.*, 1965) and, in children, by stress of the investigation (Buchanec, 1972).

The disparities that have been discussed emphasise the importance of basing treatment on all relevant considerations and not merely on anatomical or physiological abnormalities, as even severe reflux does not always herald a poor outcome (Filly *et al.*, 1974).

It is appreciated that the technique of renography used in this investigation in 1968 has long been surpassed by more accurate methods involving less radiation hazard, but even this simple method predicted which patient needed further radiological assessment. The joint results of renography and radiography identified those needing careful surveillance and energetic treatment.

Conclusions

1. An abnormal renogram is a non-specific finding that is an indication for further radiological investigation.
2. Abnormal renogram and radiograms in the same patient identified those who were potentially "at risk", and needed careful surveillance and energetic treatment.
3. Where the renogram was normal, the long-term outlook with conservative management was good, even when reflux was shown at the initial MCUG. On this basis it could be used as a screening test.
4. The radiation hazards and psychological trauma of multiple urinary tract radiography in childhood are further reasons for considering renography more widely as a screening test in children.
5. Renography may be useful in assessing the effectiveness of conservative treatment.

Summary

Many radiological methods are used in investigating urinary tract problems in children, and some are poorly tolerated. The simplest and most acceptable technique is isotope renography. Its value has been assessed in predicting the outcome of urinary tract problems in 91 children over the age of 2 years presenting consecutively over a period of 3 months.

The results of initial assessment by renography and radiography have been compared with the final clinical assessment 7 years later.

35 patients were identified as being "at risk" and all of these had abnormal renograms and radiograms.

Normal renography was found unexpectedly in some patients with severe reflux but with a good final result.

It is concluded that renography can be used to screen children with urinary tract infection, thereby excluding the less acceptable radiological investigations unless the renogram is abnormal.

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The Authors

M. Brock, FRCR, Senior Registrar in Radiodiagnosis.
R. C. L. Feneley, FRCS, Consultant Urologist.
E. R. Davies, FRCR, Consultant Radiologist.

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Short Case Report

Solitary Renal Adenoma: Benign or Malignant?

Multiple, small, symptomless, benign adenomata, varying in size from 2 to 8 mm, are a common autopsy finding in the elderly, but larger, solitary, so-called benign tumours capable of producing symptoms plus pyelographic and angiographic changes are very rare. The latter present a clinical dilemma—both in diagnosis and management.

Case Report

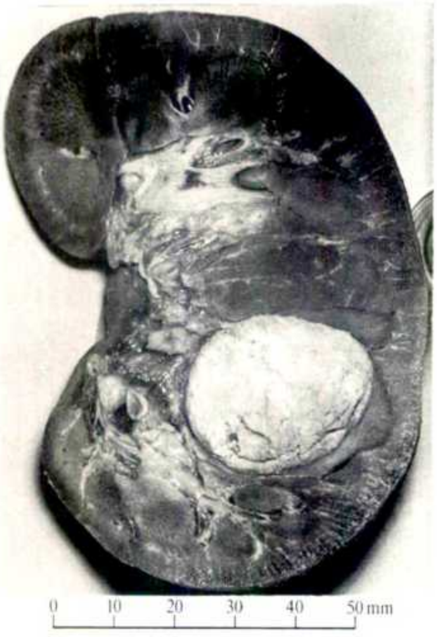
A 44-year-old woman presented with a 4-month history of intermittent painless haematuria. Clinical examination showed an otherwise healthy, slim woman with a readily palpable mobile right kidney.

An IVP, followed by a retrograde pyelogram, revealed a filling-defect in the right lower calyces. A flush aortogram, followed by selective renal angiography, showed an avascular space-occupying lesion in the lower pole, with no obvious tumour circulation. A differential diagnosis of cyst or avascular tumour was made, but because of the recurrent haematuria a cyst seemed less likely. At operation, a solid mass was easily felt within the renal substance, and nephrectomy was duly performed.

Trans-section of the excised kidney showed a clearly demarcated yellow tumour of 30 mm diameter (Fig.), and microscopic examination showed a "benign" papillary adenoma surrounded by a thick, intact, fibrous capsule with no evidence of mitosis.

Comment

Bell (1938) confidently related tumour size of less than 3 cm to high probability of a "benign" course, but this view is not upheld by Newcomb (1936) who pointed out that their structure varied little, if any, from some of those tiny symptomless carcinomas that produce precocious metastases. He is, however, uncertain whether these adenomas are truly neoplastic from their inception or whether, initially, they are merely focal areas of compensatory hypertrophy in the cells of the renal tubules. The clinician's dilemma in subsequent management has now been further compounded by Murphy and Mostofi (1970) who noted that 14% had some malignant features, and they also suggest that about 6% of true renal carcinomas may have originated in benign adenomas.



F. Konetschnik and L. Stuart Scott
UrologyDepartment, Victoria Infirmary, Glasgow

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Seasonal Variations in the Incidence of Ureteric Colic

TAHER Q. AL-DABBAGH and K. FAHADI

Department of Medicine, College of Medicine and Department of Mathematics and Statistics, College of Science; University of Mosul, Mosul, Iraq

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Increased incidence of urolithiasis during the hot season of the year was reported from many localities (Butt, 1952; Prince, Scardino and Wolan, 1956; Bateson, 1973). Prince *et al.* and Bateson studied *small* "recently formed" stones that presented clinically as ureteric colic so as to validate the aetiological significance of the hot season by blaming urine concentration from dehydration.

While practising in a locality with a high prevalence of urolithiasis (Al-Dabbagh and Mustafa, 1973), a particularly high incidence of ureteric colic was observed during the autumn. This led us to review our hospital records to try and define the precise relationship between climate and attacks of ureteric colic through statistical analysis. So far, none of the available reports could define a statistical correlation between ureteric colic and climatic phenomena.

Patients and Methods

We reviewed retrospectively the records of the single general hospital in the province (Mosul Republican Hospital) for patients with ureteric colic. We studied the records of the Medical Section for 10 years from 1963 to 1972. As for the Surgical Section, records earlier than 1969 were found grossly deficient; the satisfactorily available records of 1969-72 were studied only. We confined our study to males because, apart from reasons to be discussed later, males are exposed to climatic phenomena more than females. The quality of radiograms was such that small stones were seldom visualised; immediate intravenous pyelography was not a normal procedure. Stones that required surgical consideration were not included in an attempt to confine our study to recently formed stones.

The records of 1097 male in-patients with a discharge diagnosis of ureteric colic were thus obtained for study. Cases were distributed according to date of admission to hospital over the months of the year. The monthly totals were corrected for 30 days a month when needed.

The mean monthly data of different climatological phenomena, as recorded at the Mosul meteorological station for 30 consecutive years, were computed against the total monthly number of cases for the sake of correlation. Climatological phenomena that did not show a positive correlation were dropped aside.

Results

All cases are collectively represented in a scattergram for age and date of the year on admission to hospital (Fig. 1).

The monthly climatological data that showed a significant correlation with the monthly number of cases are presented in the Table.

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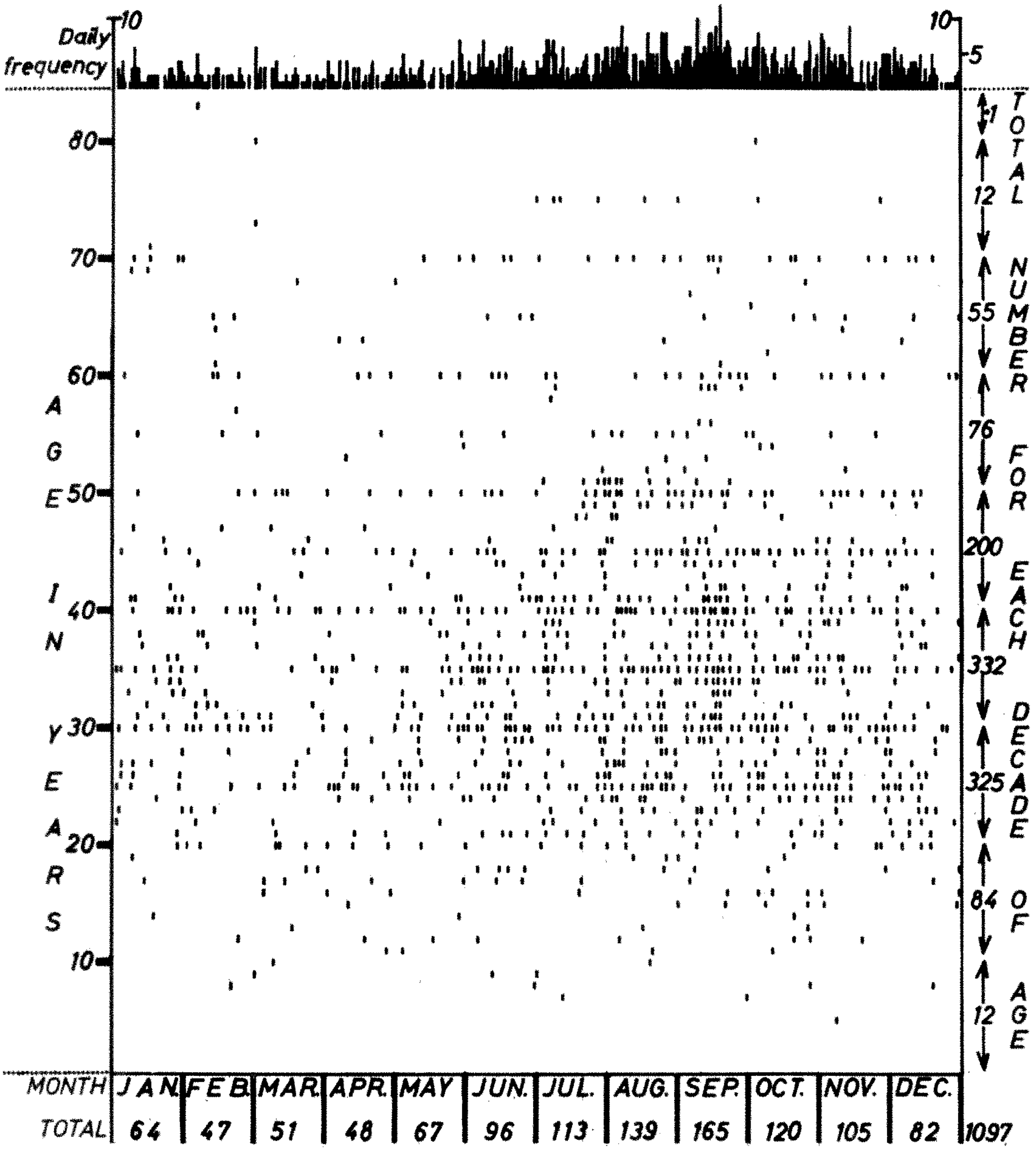


Fig. 1. Scattergram of 1097 patients distributed according to date of the year on admission to hospital and age. Each month was, of technical necessity, represented as 30 days. The 31st cases were represented with the 30th. However, in the upper strip of daily frequency the average of the 30th and 31st was plotted. In the occasional circumstance of overlap of 2 patients, the 2nd was introduced in the nearest vacant age of the same date.

Table

Data relevant to the Construction of the Regression Equation

Month of the year	Ureteric colic, observed number (corrected to 30 days per month)	Temperatures in Centigrade (average of 30 consecutive years)*				Ureteric colic estimated number
		mean minimum	mean maximum	monthly mean	difference between max. and minimum	
January	62 (64)	2·0	12·5	6·9	10·5	56
February	50 (47)	3·2	14·5	8·8	11·3	45
March	49 (51)	5·7	19·1	12·4	13·4	47
April	48	9·7	25·3	17·5	15·5	54
May	65 (67)	14·3	33·1	24·1	18·8	68
June	96	18·6	39·5	30·4	20·9	90
July	109 (113)	22·2	43·4	33·9	21·2	114
August	135 (139)	21·1	43·4	32·7	22·3	137
September	165	15·8	38·9	27·2	23·1	146
October	116 (120)	10·8	31·6	20·3	20·8	132
November	105	6·8	22·2	13·3	15·4	107
December	79 (82)	2·8	14·7	8·2	11·9	82

* Quoted from "Climatological data", Meteorological Department, Ministry of Communications, Republic of Iraq.

The correlation is shown in the following regression equation: $N_{est} = \bar{N} - 3{\cdot}1022\,(T_{max} - \bar{T}_{max}) + 5{\cdot}5548\,(T_{i-1} - \bar{T}) + 2{\cdot}8291\,(D_i - \bar{D})$. Where N_{est} = number of patients estimated in any month over 10 years; $\bar{N}$ = average monthly number of patients for 10 years = 90; T_{max} = mean monthly maximum temperature of the month concerned; $\bar{T}_{max}$ = monthly average of mean maximum temperatures = 28·18°C; T_{i-1} = mean temperature of the preceding month; $\bar{T}$ = yearly average of mean monthly temperatures = 19·64°C; D_i = difference between mean maximum and mean minimum temperatures of the month concerned; $\bar{D}$ = monthly average difference between mean maximum and mean minimum temperatures for the year = 17·1°C.

Figures 2 and 3 represent further results of relevance.

Discussion

The vast majority of our patients, if not all, should have had stone colic for the following reasons:

(1) Ureteric colic, where the cause is not known, has been ascribed to stone in many recent reports (Smith, 1966; Rhind, 1967; Blackman *et al.*, 1967; Tambyah *et al.*, 1972). This proposal was the outcome of immediate intravenous pyelography in Smith and Rhind reports.

(2) The high prevalence of urolithiasis in the locality studied; constituting 22 per 1000 general hospital admissions (Al-Dabbagh and Mustafa, 1973).

(3) The exclusion of females in the study because:

- (*a*) Females are less prone to urolithiasis than males (Boyce, Garvey and Strawcutter, 1956; Burch and Dawson, 1969; Al-Dabbagh and Mustafa, 1973).
- (*b*) Colic caused by urinary tract infection ought to have been minimised as the latter is more common among females.
- (*c*) Possible diagnosis errors from such gynaecological conditions as the pain of ovulation is obviated.

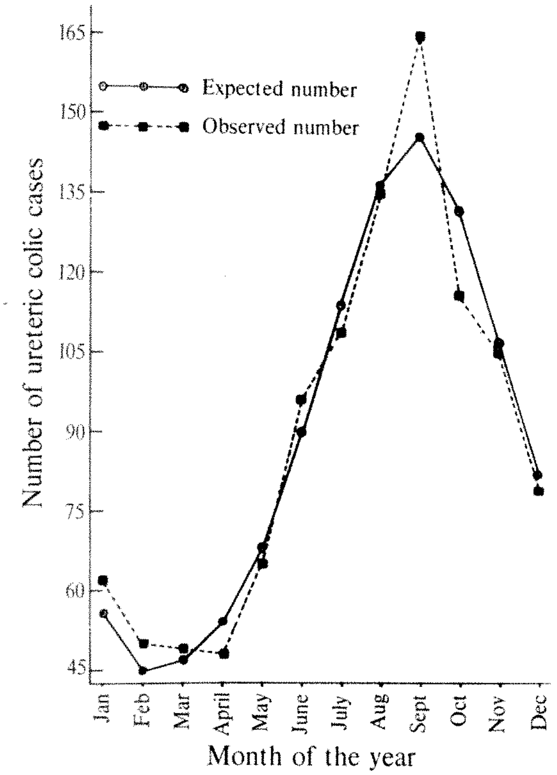
Should there remain occasional patients that did not suffer true stone colic, one presumes their even distribution throughout the year. Nevertheless, their dilution in such a large series ought not to interfere seriously with the main aim of this study—the monthly distribution of cases.

As calculated from Figure 1, the age of 85% of patients was between 18 and 55 years; the age of responsible activity. Patients were largely involved in outdoor occupations that lacked shelter from the effect of climate such as farming, driving vehicles and masonry.

The regression line for the estimated number of cases hardly differed from the actual data as shown in Figure 2. Nevertheless, their fitting together has been confirmed by using the analysis of variance. The value of *F* was counted to be 43·52—a highly significant value. Moreover, the total correlation of the observed number of cases with the relevant climatic data was counted to be 0·94, which was proved to be highly significant, too.

Interpretation of the regression equation requires the utilisation of a physiological fact that so far, and to the best of our knowledge, has not been applied in the context of urolithiasis, *viz.* cold temperatures induce diuresis through suppression of antidiuretic hormone secretion (Danowski, 1962). Frequent induction of diuresis, we believe, protects against urolithiasis because it flushes gravel should it form in the renal pelvis. Cold induced diuresis, however, could unmask silent stones of suitable sizes by mobilising them down to the ureter with the production of ureteric colic.

As obtained from the regression equation, the most influential climatic factor in the causation of colic in any month was the mean temperature of the month preceding it, bearing a coefficient of 5·5548. It means that a hot month leads to increase of ureteric colic during the subsequent



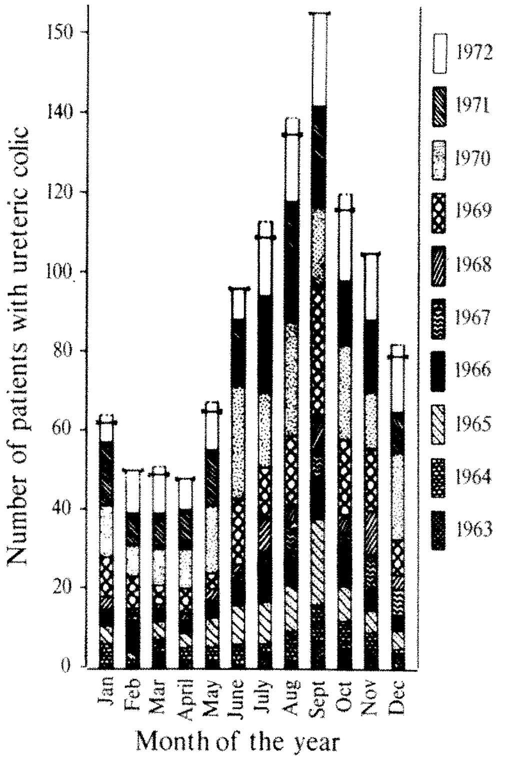


Fig. 2. Diagram representing the observed monthly total of patients for 10 years against the expected number as worked out from the regression equation to demonstrate the degree of fitting of the 2 lines.

Fig. 3. Diagram representing monthly number of patients for each of the 10 years studied. Notice the preservation of the pattern of monthly incidence all through the years. The relatively high incidence during the years 1969-72 is due to inclusion of patients from the Surgical Section (see patients and methods). The transverse line at the top of each column represents correction for 30-day month.

month; a cold month exerts the reverse effect. It is generally accepted that hot temperatures promote stone formation and stagnation in the renal pelvis from urine concentration and oliguria respectively (Smith, 1968; Straffon and Higgins, 1970), both are attributed to dehydration from excessive sweating. Thus a hot month enhances stone formation and stasis that await the chance to descend down the ureter during the subsequent month or so. Naturally, cold temperatures lead to the reverse effect. The factor of mean temperature of a preceding month is thus verified.

The factor of second importance in the regression equation is the mean maximum temperature of the month concerned. It, however, bears an inverse relation to ureteric colic. In other words, high mean maximum temperatures in a month decrease the incidence of colic during that month by a coefficient of 3·1002 and vice versa. At first glance, it seems to contradict the generally accepted views on the effect of climate. However, it would easily be accepted if we consider the effect of cold temperatures in the induction of diuresis (Danowski, 1962). Cold induced diuresis enhances mobilisation of existing stones as remarked above. High temperatures, on the other hand, lead to oliguria which enhances further growth of existing stones. Thus, the inverse relationship of mean maximum temperatures to the incidence of stone colic is verified.

The third and last factor of significance in the regression equation is the difference between mean maximum and mean minimum temperatures of a month; the wider the difference, the higher the incidence of colic by a coefficient of 2·8291. This, we believe, reflects the degree of protection from cold; the wider the difference in diurnal temperatures, the less is the protection and the more is the induction of cold induced diuresis. This is borne out by the clinical observation that cold spells during the hot season are associated with increased occurrence of ureteric colic. Moreover, the observed number of cases during September differs from and exceeds the estimated number for any other month as shown in Figure 2. We attribute it to increased exposure to cold brought by the time-honoured local habit of people in sleeping on the roof from early June to late September. It is usual to sleep without coverings as it is hot at time of going to bed. The temperature falls during the early hours of the morning; chilly degrees are seldom reached between mid-June and late August but are commonly reached during September. September has the widest gap between maximum and minimum temperatures among all months of the year (see the table). Hence, the habit of sleeping on the roof in September, a month characterised by hot evenings and chilly nights, leads to the descent of too many stones down the ureter by spells of cold-induced diuresis as to exceed the figure estimated by applying the regression equation. In October, on the other hand, people sleep in sheltered places. Exposure to cold thus decreases although it is cooler than September. One could conclude that, should the local habit of sleeping on the roof not have existed, an even more precise fitting of the regression line with the actual data would have been obtained in Figure 2. The above discussion attests the role of the difference between maximum and minimum temperatures in the production of ureteric colic.

Comparing our figures with those of previous reports (Butt, 1952; Prince *et al.*, 1956; Bateson, 1973), ours show more striking variation in the monthly or seasonal incidence of ureteric colic. The reasons for this are likely to be the following:

(1) The wider variation in daily and seasonal temperatures in our locality as compared to places from which other reports were derived.
(2) The generally less developed status of the community under study and thus the stronger influence of climate on the people.
(3) The relative rarity of drinking alcohol in our locality; alcohol could lead to the same effect as cold in inducing diuresis.

Conclusions

The implications of the present study are many:

(1) The relationship of stone colic to atmospheric temperatures is not a simple one. Though the factor of stone formation in hot climates is well recognized, the factor of stone descent,

and hence the pain of ureteric colic, by cold-induced diuresis is being considered for the first time in this context. This explains the previous deadlock in attempting to establish a statistically significant correlation between temperature variations and urolithiasis (Blacklock, 1969). None of the available reports could progress beyond the exposition of figures of monthly or seasonal incidence of colic against monthly temperatures.

(2) The ever-increasing prevalence of upper urinary tract calculi with industrialisation in such developed communities as exemplified by Norway and Britain (Anderson, 1969) may be explained on the evidence laid in this study thus: in these countries with generally cold weather, if other factors remain the same, exposure to cold and cold-induced diuresis would decrease as a result of more efficient heating of places of work and residence that accompanied industrialisation. In other words, tiny gravel that forms in the renal pelvis among people in such countries has a poorer chance to descend asymptomatically down the ureter through deprivation from cold-induced diuresis. Lack of diuresis would give a better chance for growth of the piece of gravel to an established renal stone. Likewise, one may anticipate that industrialisation of communities with a generally hot climate would not be associated with increased prevalence of upper urolithiasis if the present viewpoint holds true.

(3) This study confirms the validity of the time-honoured advice on excessive drinking of water by repeated stone-formers. In point of fact, the advice may be extended to induction of prompt diuresis every now and then.

Lastly, we have to state that the effect of climate on the genesis of urolithiasis should not contradict the well-settled metabolic causes of stone formation in any way. It rather throws some light on the problem of idiopathic stone-formers. In point of fact, it opens a new approach for the study of the latter problem.

Summary

A retrospective study of 1097 male in-patients with ureteric colic was conducted to try and define the aetiological effect of climate on the disease.

The overall monthly incidence for the study period of 10 years was found, on statistical analysis to correlate with ambient temperatures thus: (1) directly with the mean temperature of the *preceding* month, (2) directly with the difference between mean maximum and mean minimum temperatures of the *same* month, and (3) inversely with the mean maximum temperature of the *same* month. The correlation was interpreted on the basis that hot ambient temperatures promoted stone generation whereas cold ones promoted stone descent through cold-induced diuresis. This trend, among its other implications, could pinpoint the reason for the increase in nephrolithiasis with industrialisation.

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The Authors

Taher A. Al-Dabbagh, MRCPE, Assistant Professor.
K. Fahadi, PhD.

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Short Case Report

Multicystic Kidney following Uretero-colic Diversion

The development of a unilateral multicystic kidney in a patient following uretero-colic diversion prompted us to review the literature on the subject. There appears to be no reported case of multicystic disease following any type of urinary diversion.

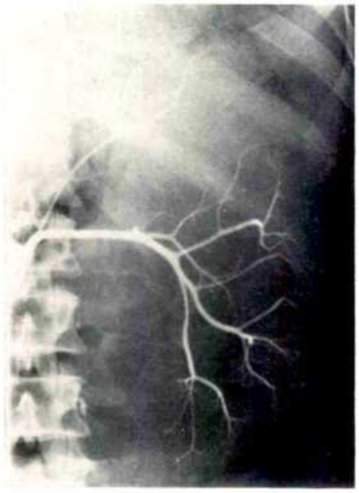
Case Report

A 34-year-old farmer was found on investigation for haematuria to have a bladder lesion suspicious of carcinoma *in situ*. Resection and diathermy of the lesion was carried out, and histology confirmed the diagnosis of carcinoma *in situ* (TIS,) without any deep invasion. An excretion urogram showed a normal upper urinary tract. Repeated cystoscopic examinations at 3-month intervals over the next 3 years revealed similar appearances on 8 occasions. These were either resected or diathermised. In February, 1969, the histology showed evidence of submucosal invasion, and a total cysto-prostatectomy with uretero-colic diversion of urine was carried out. The histology report on the bladder showed evidence of deep invasion into muscle (P3). An excretion urogram 1 month later showed a slight dilation of the right urinary tract, with a normal left urinary tract. In April, 1972, an intravenous urogram showed a space-occupying lesion in the left kidney, which, on exploration, was found to be a simple benign cyst at the hilum. This was excised. Further cysts were again seen on an intravenous urogram in May, 1974, and a percutaneous cystogram demonstrated the kidney to be multicystic. On examination in August, 1975, a large left renal mass was palpable, and a left selective renal arteriogram showed a large multicystic kidney without any apparent functioning renal tissue (Fig.). A left thoraco-abdominal nephrectomy was carried out, and the histology report confirmed a huge benign multicystic kidney.

The patient remains well, without any evidence of recurrence of his vesical neoplasm, and a recent intravenous urogram shows the right kidney to be normal.

Comment

The aetiology of multicystic kidney is not clearly understood. In his original experimental work, Hepler (1930) showed that localised urinary obstruction plus vascular impairment would lead to cystic disease. Spence (1955), in a review of 15 cases, thought that this lesion was congenital and considered it harmless, provided that the other kidney was normal. Charlton and Evans (1966) felt that ureteric obstruction was the most important pathogenetic factor. We feel that a combination of renal infection associated with obstruction may have been responsible for the cystic disease in the kidney of this patient.



J. M. Smith and J. D. O'Flynn
Urological Department, Meath Hospital, Dublin Ireland

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Seasonal Variations in Urinary Crystals

P. C. HALLSON and G. ALAN ROSE
St Peter's Hospitals and Institute of Urology, London

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Only in recent years have attempts been made to study urinary crystals at body temperature and to relate the findings to the occurrence of renal calculi (Dyer and Nordin, 1967; Robertson, Peacock and Nordin, 1971). More recently still Hallson and Rose (1977) have reported differences in crystalluria between normal subjects and stone-formers with idiopathic hypercalciuria and upon the effects of treatments by the patients on the crystalluria. In the latter paper, crystalluria was taken as an indicator of urine super-saturation with the material from which the crystals were composed.

Seasonal variations in urinary composition have recently been reported. Urinary calcium was found in Leeds to be higher in summer than in the winter (Robertson *et al.*, 1974) but this is not so in London (Hallson, Kasidas and Rose, 1977). Urinary oxalate is higher in the summer than in the winter both in London (Rose and Hallson, 1975; Hallson, Kasidas and Rose, 1977) and in Leeds (Robertson *et al.*, 1975). It was therefore thought of interest to find out how urinary crystals varied between summer and winter. To this end, the data of Hallson and Rose (1977) were extended and re-examined for seasonal variations. In addition, urinary composition was also examined to see if any changes in crystal occurrence could be explained by changes in urinary composition.

Methods

The subjects were either normal volunteers or stone-formers with idiopathic hypercalciuria as defined by Rose and Harrison (1974). The patients were either on no drug treatment or receiving bendrofluazide and/or cellulose phosphate (Rose and Harrison, 1974). All the studies were made during the period October 1974 to August 1976 inclusive. The patients used for the crystal studies were also used for the 24-hour urine collections, although these did not necessarily coincide, and not all patients had both types of investigation. Most patients attended the metabolic out-patient clinic on several occasions over the period and some were investigated several times. In the case of crystal studies the urine samples were either random mid-morning out-patient specimens without any patient preparation, or first urine passed on rising in the morning (EMU1), or the next specimen (EMU2) obtained after a dry breakfast and prior to any fluid intake. These urine samples were passed directly into pre-warmed thermos flasks (Hallson and Rose, 1976). The random and EMU2 samples were transported immediately to the laboratory. In the case of EMU1 samples there was sometimes a delay of up to 2 hours in their reaching the laboratory and bacterial growth could have commenced during this period. It is thought, however, that there would not be sufficient growth in this time to affect urine composition significantly and this point of view is supported by the finding that bacteria were never observed in the centrifuged deposits.

These urine samples were studied at 37°C qualitatively by light microscopy and quantitatively by Coulter Counter (Hallson and Rose, 1976). 24-hour urinary collections were analysed for calcium by flame-photometer (emission at first and atomic absorption later), creatinine by Auto Analyser II Jaffe technique, oxalate by the enzymatic method of Hallson and Rose (1974), magnesium by atomic absorption flame-photometer and phosphate by Auto Analyser II by standard method.

The information on mean ambient temperature was kindly supplied by the London Weather Centre. Spring was considered to be March to May, summer as June to August, autumn as September to November, and winter as December to February.

Results

The percentages of all the individual urine samples examined for crystals that showed oxalate and phosphate crystalluria during each of the 4 trimesters are shown in Figure 1. This figure also shows the mean creatinine concentrations of the same urine samples in the 4 trimesters. Figure 2

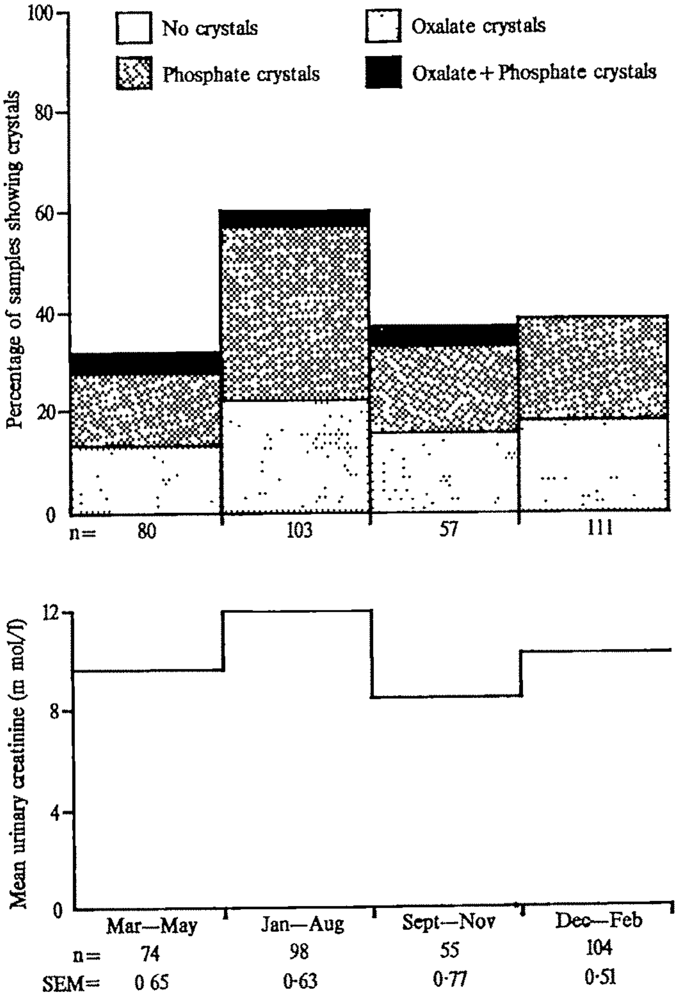

Fig. 1. Effect of season of the year upon the incidence of phosphate and oxalate crystalluria and upon mean creatinine concentrations of the same urine samples. The patients all had idiopathic hypercalciuria and were undergoing long-term study, and some were receiving treatment with thiazide and/or cellulose phosphate. The number of samples and standard errors of the mean are indicated by "n" and "SEM" respectively.

shows for the same 3-month periods the variations in mean ambient temperature and in mean chemical composition of 24-hour urinary collections made over the same period of time. The data from which this figure was prepared are summarised in the Table. The data on urinary crystals from Figure 1 have been broken down according to the treatment given in Figure 3, and according to the time of the bladder emptying in Figure 4.

In preparing Figures 1 and 2 it has been necessary to pool results from all patients whether treated or untreated. In theory such a procedure could bias the results if a higher proportion of one group of patients occurred in any one month. Such bias is thought to be extremely unlikely because selection of patients was determined only by ability to provide the urine sample when required and bore no relation to treatment or time of year. In fact the lack of bias due to treatment is revealed by Figure 3.

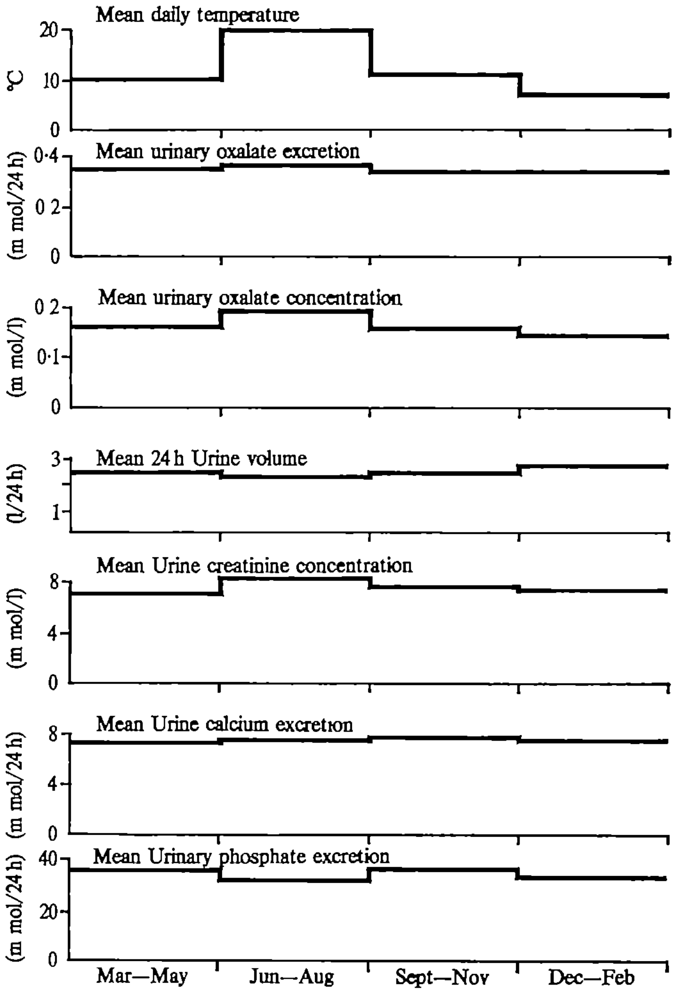

Fig. 2. Effect of season of the year upon mean ambient daily temperature and upon chemical composition of 24-hour urine samples from a series of stone-forming patients undergoing prolonged study for idiopathic hypercalciuria. This data is further analysed in the Table.

Table

Effect of Season of the Year upon Chemical Composition of 24-hour Urine Samples of Stone-formers. An Analysis of the Data from Figure 2

		Mar-May	June-Aug	Sept-Nov	Dec-Feb
Mean daily temperature °C		9·7	19·5	10·6	7·3
Oxalate excretion, mmols/24 hours	Mean	0·34	0·36	0 32	0·32
	No.	202	262	193	193
	S.D.	0·140	0·144	0·143	0·141
Oxalate concentration, mmol/l	Mean	0·159	0·195	0·163	0·144
	No.	201	262	193	193
	S.D.	0·09	0·11	0·09	0 07
Urinary volume, l/24 h.	Mean	2·35	2·18	2·23	2·40
	No.	202	262	193	193
	S.D.	0·93	1·02	0·87	0·77
Creatinine concentration, mmol/l	Mean	7·15	8·19	7·54	7·24
	No.	201	253	193	191
	S.D.	3·24	4·31	3·49	3·59
Calcium excretion, mmol/24 hours	Mean	7·26	7·29	7·63	7·25
	No.	194	243	193	191
	S.D.	3·15	3·48	3·58	3·10
Phosphate excretion, mmol/24 hours	Mean	35·36	32·59	35·33	33·8
	No.	170	201	163	169
	S.D.	11·1	11·6	12·7	13·3
Creatinine excretion, mmol/24 hours	Mean	14·9	14·8	14·7	15·7
	No.	201	253	193	191
	S.D.				

Discussion

Figure 1 shows that the incidence of crystalluria in all the samples of urine of all the stone-formers varied only narrowly between 32% and 38% during September to May inclusive, but rose dramatically to 60% for the summer trimester, June to August. This raised incidence of crystalluria in the summer was due to rises in the incidence of both phosphate and oxalate crystals but with a greater rise in the former. The reasons for this increased incidence of crystalluria in the summer months could be multiple, but certain factors have emerged as a result of the present study. Firstly, urinary volume might fall in the warmer summer months but Figure 2 and the Table show that the mean 24-hour urinary volume in a series of patients undergoing repeated out-patient observations did not greatly alter during the summer. Despite a clear rise in ambient daily temperature from 7°C in the winter to 19°C in the summer, the fall in mean urinary volume was only from 2·4 to 2·15 litres/24 hours and this is not statistically significant. However, the urinary crystal studies were performed not on 24-hour urinary saves but on individual bladder emptyings and Figure 1 shows that creatinine concentrations in the samples showed a clear peak in the summer months. Thus the mean creatinine concentration was 11·9 mmol/24 hours for the summer months and 9·4 mmol/24 hours for the rest of the year. The possibility that the composition of urinary constituents might also change during the summer months should also be considered. Reference to Figure 2 shows that 24-hour urinary calcium did not change from season to season and this is in keeping with results previously reported from this laboratory (Hallson, Kasidas and Rose, 1977). Urinary oxalate did, however, show a rise in the summer months, both in total 24-hour output as previously described (Hallson, Kasidas and Rose, 1977) and also a larger and statistically highly significant rise in oxalate concentrations. It is, therefore, thought that the rise in oxalate crystalluria in the summer is explained by the increased concentration occurring in the individual urine samples together with raised urinary oxalate excretion concentration. Urinary phosphate did not change from season to season and the increase in phosphate crystalluria in the summer months can be explained only by the general increase in concentration as illustrated by the raised creatinine concentrations.

Three different types of urine collections are in fact summated in Figure 1 but are shown separately in Figure 4. It can be seen that while it is still true that for each type of urine collection the incidence of crystals is highest in the summer trimester, there are some important differences. In the overnight urine collections (EMU1) the summer rise in crystal incidence is wholly attributable to phosphate crystals whereas in the random (mid-morning) urine samples the rise is almost entirely due to oxalate crystals. This observation seems surprising in view of the tendency of mid-morning urine samples to have a higher pH (alkaline tide) than overnight samples and this should lead to an increased incidence of phosphate crystals mid-morning (Hallson and Rose, 1977). The explanation may be that during the morning urinary oxalate rises to a peak (Zarembski

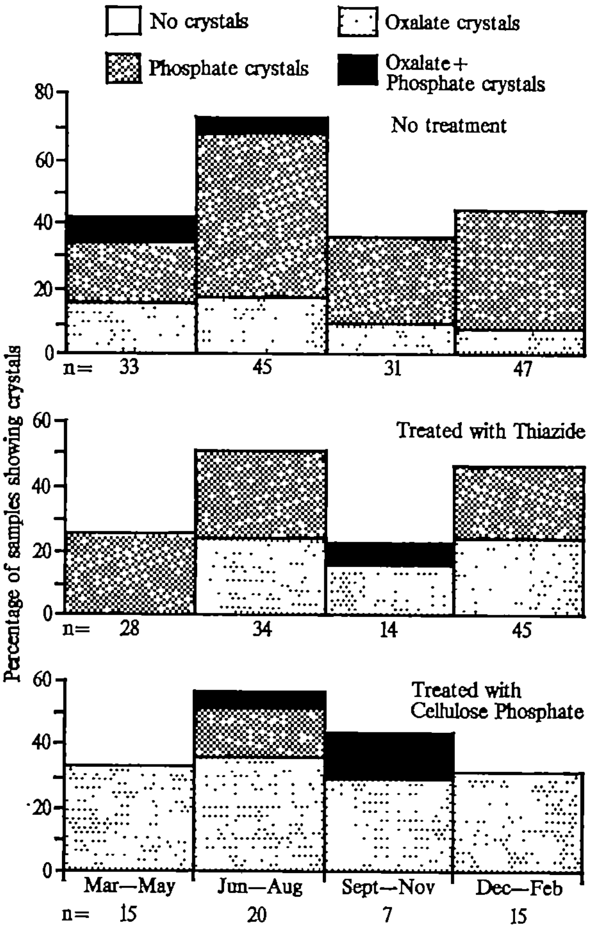

Fig. 3. Effect of treatment of stone formation with idiopathic hypercalciuria upon the seasonal incidence of oxalate and phosphate crystalluria. The number of samples in each group is shown by "n".

and Hodgkinson, 1969) whereas the urinary phosphate excretion is low mid-morning, peaks later in the day and is high during the night (Heaton and Hodgkinson, 1963). The seasonal variations become rather blurred in the case of the EMU2 urine samples, perhaps because in order to obtain these samples the patients were asked to undergo moderate dehydration and this could have masked the effect of seasonal dehydration from raised ambient temperature. It should be noted, however, that the crystal incidence rose to as high as 80% for these samples during the summer months.

3 different treatments are also summated in Figure 1 and these should be considered separately. In Figure 3 it can be seen that the summer rise in incidence of crystalluria is greatest in the patients with "no treatment" reaching 74%, and this rise is almost entirely attributable to increased phosphate crystals. Patients treated with cellulose phosphate showed a high incidence of oxalate crystals which was rather constant during all seasons of the year, while phosphate crystals alone were seen only in the summer months. In the thiazide-treated patients it is hard to see a clear pattern of seasonal changes.

There now can be little doubt of the relationship between urinary volume and renal stone formation. Several groups have shown that a hot environment leads to increased stone incidence. (review by Rose, 1968). Furthermore, Frank and de Vries (1966) showed in a prospective study that raised fluid intake in a hot environment reduced the incidence of stones. The studies reported in this paper provide quantitative evidence that the super-saturation of urine for calcium phosphate and calcium oxalate rises in the summer months and that this can be attributed largely to decreased urinary volume. It is of particular interest that this fall in urinary volume was detected only in the urine samples used for the crystal studies and not in the 24-hour urinary collections. This is probably because all the stone-formers had been instructed to maintain their urine volumes even in the warm weather and probably did so by drinking in the day but not during the night. It therefore seems that the risk of crystal formation (and presumably of stone formation and growth) is greatest overnight during the summer months and patients should be given appropriate advice on this point.

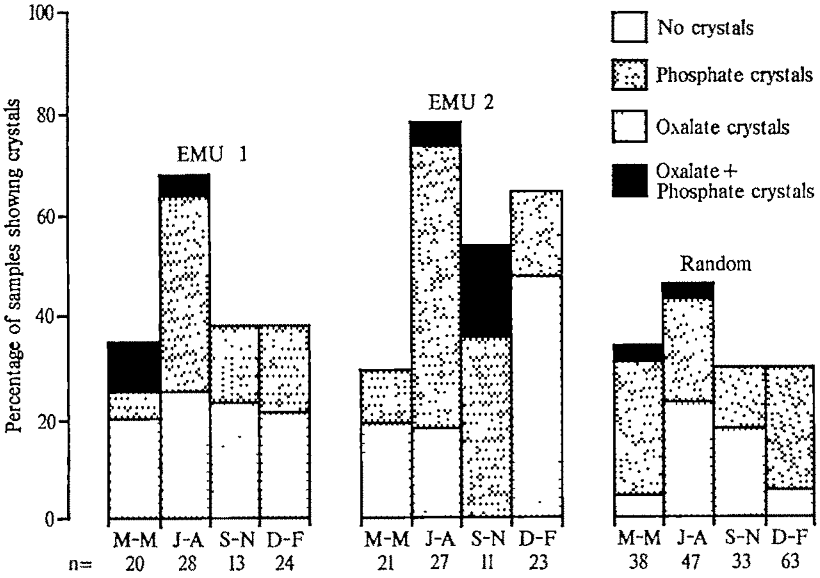

Fig. 4. Effect of season of the year upon incidence of crystalluria in the 3 different types of urine collections. EMU1 was over-night urine, EMU2 followed mild dehydration and random was mid-morning (see text).

The role of oxalate in crystal formation is also of special interest. Although the rise in the total urinary oxalate during the summer months is shown in Figure 2, it is not as impressive as previously reported from this laboratory (Rose and Hallson, 1975; Hallson, Kasidas and Rose, 1977). The summer rise in urinary oxalate has decreased each summer since we first observed it in our patients. This is probably because in many cases where the rise has been noted the individual has been questioned about his food habits and a source of dietary oxalate identified and the patient instructed to avoid it. In fact, a rise in urinary oxalate has usually been associated with rhubarb in the spring, spinach or strawberries in the summer and with beetroot in the late summer. Since this study is longitudinal and long-term, many patients who originally showed the summer rise in urinary oxalate, no longer do so and this must be regarded as a gain.

It is still not clear whether super-saturation of urine with calcium oxalate is more or less important for stone formation than super-saturation with calcium phosphate and the present study does nothing to resolve this question. It may be stated, however, that if calcium phosphate is the more important, then the observations in Figure 4 indicate that the patients are at greatest risk of stone formation overnight, whereas if calcium oxalate super-saturation is the more important then the greater risk appears to be in mid-morning. The bad effect of mild dehydration is also apparent in Figure 4, which shows that the specimens obtained following a dry breakfast had a raised incidence of both phosphate and oxalate crystals.

Summary

Individual urine samples from normal subjects and stone-formers with idiopathic hypercalciuria have been examined for crystals both qualitatively and quantitatively at 37°C.

The group as a whole showed a rise in incidence of urinary crystals in the summer months of June to August inclusive. This rise was seen most clearly in overnight urines, collected on rising in the morning, and the patients appeared to be at risk overnight during the summer.

In the untreated patients the summer rise in incidence of phosphate crystals was quite dramatic but was only small in the cellulose phosphate treated group, who showed a rather constant and raised incidence of oxalate crystals right through the year.

Seasonal crystal incidence has been compared with seasonal changes in urinary composition. The rise in crystal incidence during the summer was associated with increased creatinine concentration in the same urine samples and with increased oxalate concentration in 24-hour urine collections.

We would like to express our thanks to Sister McKenna for helping with the urine collections, to the Post-Graduate Medical Federation of London for having donated the Coulter Counter, to the St Peter's Research Trust and Institute of Urology for much financial support.

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A Technical and Clinical Evaluation of the Disa Uroflowmeter

D. ROWAN, A. L. MCKENZIE, S. G. MCNEE and E. S. GLEN

Department of Clinical Physics and Bio-Engineering, West of Scotland Health Boards, and Urodynamic Clinic, Southern General Hospital, Glasgow

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Over the last 20 years several methods of measuring urinary flowrate have been described. These have included (1) the continuous measurement of the weight of urine voided (Kaufman, 1957; Backman and Von Garrelts, 1963; Bowley and Legg, 1971), (2) the measurement of the flowrate of air displaced from a closed vessel in which the urine was collected (Holm, 1962; Palm, 1968; Gierup, Ericsson and Okmian, 1969), (3) the measurement of the clearance of a radioisotope from the bladder during micturition (Winter, 1964; Strauss and Blaufox, 1970; Rowan, Millar and Alexander, 1972) and (4) the use of an electromagnetic flowmeter attached to a collecting funnel (Cardus, Quesada and Scott, 1963).

Following their finding that the urinary stream breaks up into drops within a short distance of the external meatus, Zinner *et al.* (1969) designed an instrument called a drop spectrometer. By means of this apparatus, the drop sizes and velocities were measured and hence the instantaneous

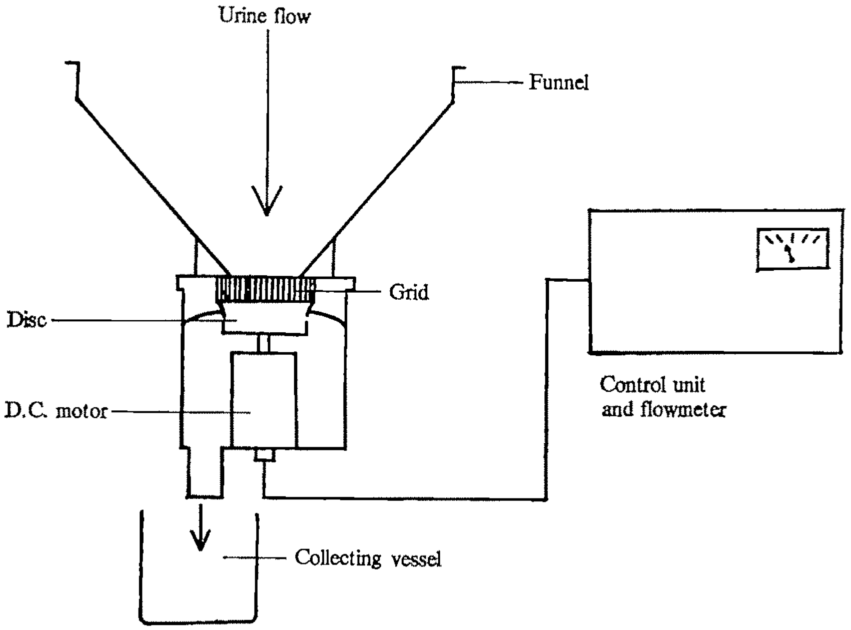


Fig. 1. Schematic diagram of Disa uroflowmeter.

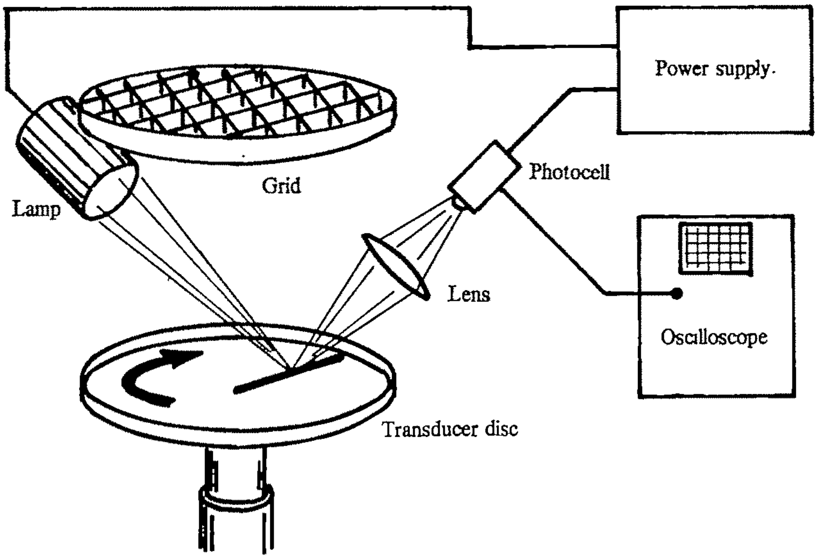


Fig. 2. The experimental arrangement used to determine the variation in rotational speed of disc at different flowrates.

flowrate could be computed. The sophistication and the expense of the equipment involved, however, has limited its application to a few research centres.

About 4 years ago, a new principle was introduced in a uroflowmeter which was manufactured by Disa Elektronik A/S (Denmark) and used in a number of departments in this country. In this instrument (Fig. 1), the flow transducer consists of a lightweight disc with a rim which is fitted to the shaft of a vertically mounted D.C. motor housed in a cylindrical collecting chamber. During voiding, urine is directed vertically on to the rotating disc by a metal grid. When the urine reaches the circumferential velocity of the disc, it is ejected into the transducer chamber and then discharged into a collecting vessel. The speed of rotation is controlled by the output of a servo-amplifier and the operation of the instrument is based on the theory that the amount of electrical energy required to maintain the disc velocity constant is proportional to the urine mass flowrate. Although reports on the clinical use of this equipment have appeared in the literature (Debled, 1973; Tammen, 1975), little detail has been published on its technical performance. A technical and clinical evaluation was therefore carried out.

Methods and Materials

The variation in the rotational speed of the disc with increasing flowrate was investigated using the experimental arrangement illustrated in Fig. 2. A black line was stencilled along one of the radii of the disc. By employing the lighting and optical system shown, a pulse was detected from the photocell for each revolution of the disc. The time between pulses was measured on the oscilloscope and hence the rotational speed was obtained. For this experiment, the normal funnel arrangement was dispensed with and the grid was specially mounted on a stand to permit the use of the lamp and lens.

The performance of the completely assembled equipment was then investigated by measuring:

(1) the linearity of the flowrate calibration when the stream was directed vertically on to (*a*) a fixed position on the collecting funnel and (*b*) the axis of rotation of the disc;

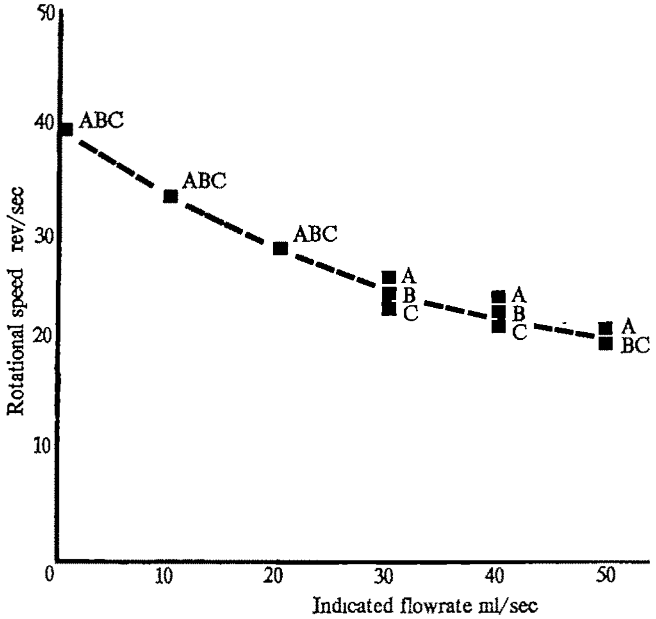
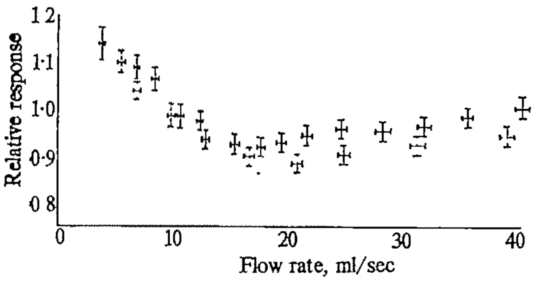


Fig. 3. Variation in rotational speed of disc with flowrate. A, with grid in place, stream directed on to disc 1 cm from the centre. B, same conditions as in A except that grid was removed. C, with grid removed, stream directed on to centre of disc.



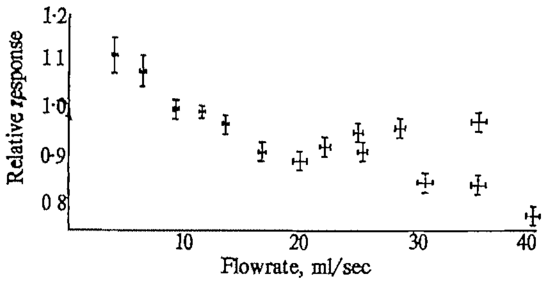


Fig. 4. Variation in response to constant flow directed on to fixed position on funnel (+ transducer 1; + transducer 2).

Fig. 5. Variation in response to constant flow directed on to point close to axis of rotation (+ flow between grid intersections; + flow on to grid intersections).

(2) the variation in response to a constant flowrate as a function of the radial displacement of the point of impact from the axis of rotation;

(3) the transient effect due to change of direction of the stream during constant flow conditions.

In all these tests, constant flowrates of water were obtained from a constant head tank, the height of which was adjustable. The flowrate indicated on the flowmeter was noted and confirmed by an independent pen recorder connected to the flowmeter output. For each set of flow conditions, 4 readings were taken and the means and standard deviations derived. The density control was set at "1·0" and the damping control was in the "ON" position giving an instrument time constant of 0·5 sec.

Results

(a) *Technical Evaluation*

As indicated in Fig. 3, there was a marked reduction in the disc rotational speed as the flowrate was increased. Further investigation revealed that this non-linearity was reduced, although not eliminated, by electronic compensation within the instrument.

When the water stream was directed vertically on to a fixed position on the collecting funnel, it was found that the calibration was non-linear, particularly at low flowrates (Fig. 4). A second transducer, tested under similar conditions, gave comparable results. When flow was directed vertically between the grid intersections close to the axis of rotation of the disc, again a similar characteristic was obtained (Fig. 5). However, if the stream was moved marginally so that it struck the intersections, then significant errors at high flowrates were recorded. These results indicate that the characteristic is primarily a function of the electronics and not of the transducer.

The response to a constant flowrate, as a function of the radial displacement of the point of impact of the stream from the axis of rotation, is shown in Fig. 6. For flowrates less than 12 ml/sec, the response was independent of radial displacement. At higher flowrates, a marked dip occurred in the characteristic which was a maximum when the point of impact was at the edge of the disc. At flowrates in excess of 25 ml/sec, the dip was more marked if the stream was moved slightly to strike the grid intersections. We have shown that, if the transducer is modified so that the grid aperture leading to the disc is reduced to 1·5 cm diameter, the dip is largely eliminated.

In common with many other methods of measuring flowrate, the Disa system employs a funnel to direct the stream to the transducer. Hence, there is a significant delay between the flowrate

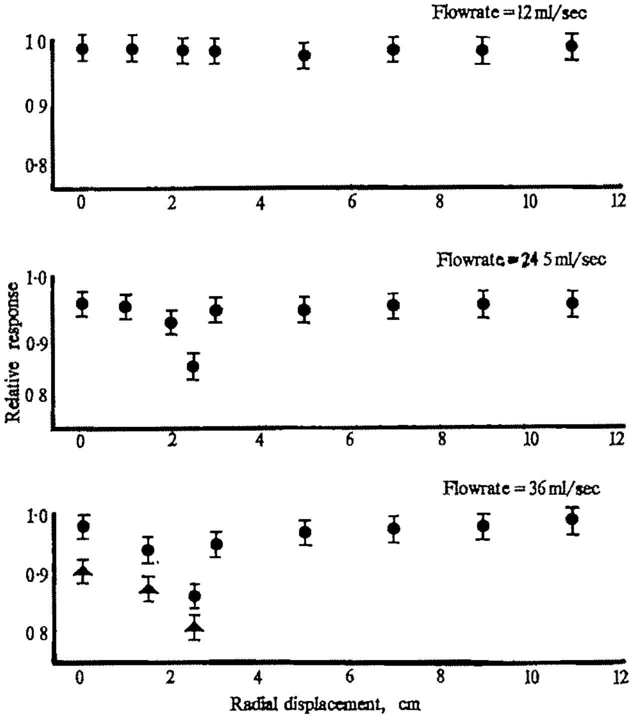


Fig. 6. Variation in response as a function of radial displacement of point of impact from axis of rotation (● flow between grid intersections; ▲ flow on to grid intersections).

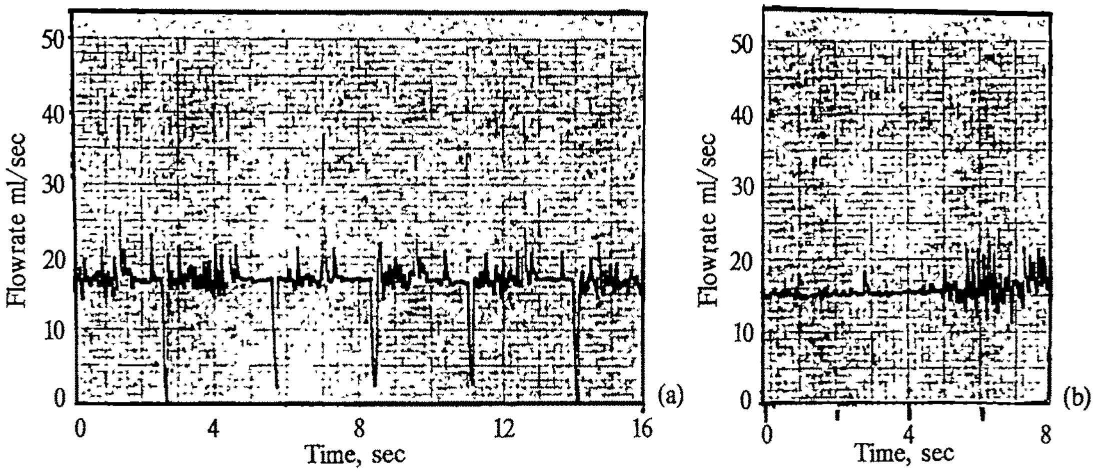


Fig. 7. Transient response to change in stream direction during constant flow conditions. (*a*) Rapid movement; (*b*) gradual movement.

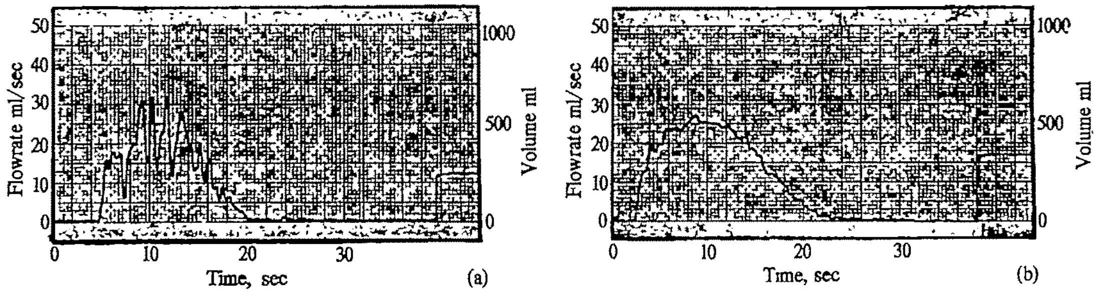


Fig. 8. Flow curve recorded from male patient. (*a*) When instructed to vary direction of urine stream; (*b*) when instructed to void on to fixed position on funnel.

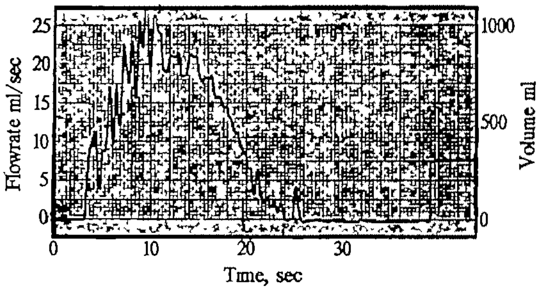


Fig. 9. Flow curve obtained from male patient to whom no special instructions were given.

measurement and the actual micturition event. If this lag was fixed, then a simple correction could be made to the time scale. However, the lag varies with the angle at which the stream strikes a given point on the funnel, the actual point struck by the stream, the stream velocity and the degree of swirling present (Zinner, 1971).

Fig. 7 shows the transient effects due to changes in direction of the stream under constant flow conditions. These recordings were made with the damping switch in the "OFF" position, giving an instrument time constant of 0·1 sec. The amplitude of these errors depended on the rate at which these movements took place. The peaks occurred when the stream was moved into the centre, the troughs when it was moved away from the centre. However, even if the rate of movement was gradual, these errors were still significant at this time constant setting. For this reason, all clinical measurements were made with an instrument time constant of 0·5 sec.

(b) *Clinical Evaluation*

The flow curve obtained from a male patient who was instructed deliberately to vary the direction of the urinary stream during voiding is illustrated in Fig. 8a. The characteristic peaks and troughs are clearly seen. The total volume voided is also indicated on the recording. In contrast, Fig. 8b is a recording from the same patient who was asked to direct the stream, as far as possible, on to a fixed position on the funnel. Obviously, changes in direction still took place, particularly towards the end of micturition. However, the rate of change appeared to be sufficiently slow that no marked peaks or troughs were recorded.

The flow pattern shown in Fig. 8a is, of course, artificial. However, a recording from a male patient, to whom no special instructions were given and who voided in privacy, is shown in Fig. 9. The peaks and troughs at the beginning of micturition suggest stream movement rather than any physiological explanation.

Our clinical measurements emphasised the dependence of the flow pattern on the volume voided and clearly indicated that, if a flowmeter is being used in a screening test on a large number of patients, the clinician must take some trouble to ensure that there is an adequate volume in the bladder before carrying out the examination. Our results, however, showed that measurements made on an overdistended bladder can also lead to misinterpretation.

Some characteristic flow patterns were obtained. In particular, patients suffering from prostatic hypertrophy produced plateau-shaped flow curves usually with a slow initial rise to the maximum flowrate which was always markedly below normal. An intermittent flow pattern was obtained from patients who voided primarily by increasing intra-abdominal pressure. The residual urine volume in these patients was usually significant.

Conclusions

In spite of the deficiencies which exist in this flowmeter, it is still clinically useful, when used in a screening test, for identifying certain patterns of micturition, provided a time constant of 0·5 sec is used. It is recognised that, for some clinical applications, the errors at low flowrate may not be serious. However, to reduce errors at high flowrate, it is advisable to instruct male patients to avoid micturating, as far as possible, directly on to the grid, particularly at the beginning of micturition. This is not a problem with female patients who are seated during the examination. The characteristic distortion of the flow pattern due to stream movement can usually be identified and should not be misinterpreted.

It must be appreciated that, no matter which flowmeter is used, the value of isolated measurements of flowrate is limited because of the dependence of the flowrate on other factors such as intravesical pressure, volume voided and residual urine volume. In combined pressure-flow studies, the limitations of the flowmeter must be taken into account when the results are being interpreted.

Summary

This investigation reveals that there is a marked reduction in the rotational speed of the transducer disc as the stream flowrate is increased, although the non-linearity is partly reduced by electronic compensation within the instrument. The inaccuracy at low flowrates is probably unimportant in routine clinical applications. However, significant errors are recorded at high flowrates when the stream strikes the grid intersections or when the point of impact is close to the edge of the rotating disc. For these reasons, it is desirable that the patient should avoid micturating directly on to the grid.

To obtain acceptable clinical recordings, an instrument time constant of 0·5 sec must be used. Although some characteristic tracings can be identified, the clinical measurements indicate that the effects of the volume voided and stream movement must be taken into consideration when the flow patterns are being interpreted.

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The Authors

D. Rowan, MSc, CEng, MIEE, FInstP, Principal Physicist.
A. L. McKenzie, BSc, PhD, Physicist.
S. G. McNee, BSc, Physicist.
E. S. Glen, MB, ChB, FRCS, Consultant Urologist.

Request reprints from: Mr D. Rowan, Department of Clinical Physics and Bio-Engineering, West of Scotland Health Boards, 11 West Graham Street, Glasgow G4 9LF.

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Short Case Report

Squamous Cell Carcinoma of the Urachus with Vesical Calculus

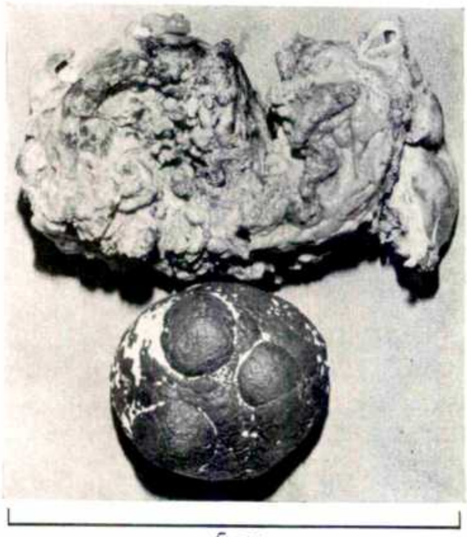
A 35-year-old male complained of dysuria and dull aching pain in the perineum for 8 months and pain and swelling in the subumbilical region for 4 months. Examination revealed a circular tender mass in the hypogastrium which was bimanually palpable. Plain X-ray of the abdomen showed a big vesical calculus. Urine culture showed a heavy growth of *E.* Coli. At operation, in addition to the vesical calculus, there was a cystic mass adherent to the fundus of the bladder. The peritoneum was opened and the cystic swelling attached to the median umbilical ligament and the dome of the bladder was excised along with the fundal portion of the bladder. The patient has been symptom free for 9 months.

The stone was 6 cm in diameter and weighed 100 g. The cystic swelling was $11{\cdot}5 \times 6 \times 3$ cm, and contained greyish-white growth (Fig.). Microscopically it showed squamous cell carcinoma in the urachal cyst.

Comment

Out of 150 cases of urachal carcinoma reported so far, mucinous adenocarcinoma is the commonest. Rarely, transitional cell, anaplastic, mixed and squamous cell carcinomas are reported. This is the third case of squamous cell carcinoma and first to be associated with urinary calculus.

Carcinoma situated in the dome of the bladder, revealing muscular or extravesical involvement, without adjacent cystitis glandularis and without adenocarcinoma elsewhere, may be of urachal origin (Beck, Gaudin and Bonham, 1970). Haematuria, abdominal pain and abdominal mass are the commonest complaints. Some are found during autopsy (Rubell and Porges, 1972). Aggressive surgical treatment has given the best results so far (Whitehead and Tessler, 1971). In general the prognosis is not good.



B. D. Pujari,[1] Mrs M. Phansopkar[2] and S. G. Deodhare[3]

[1] *Consultant Surgeon, Shree Hospital, Miraj 416 410,* India; [2] *Reader in Pathology, Medical College, Miraj 416 410,* India; [3] *Prof. of Pathology, Grant Medical College, Bombay 400 008,* India

Address for correspondence: Dr B. D. Pujari, Consultant Surgeon, Shree Hospital, Miraj 416 410, India.

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Physical Information in the External Urinary Stream of the Normal and Obstructed Adult Male

R. C. RITTER, A. M. STERLING and N. R. ZINNER

Department of Physics, University of Virginia, Charlottesville, Virginia; Department of Chemical Engineering, Louisiana State University, Baton Rouge, Louisiana; and Division of Urology, Department of Surgery, Martin Luther King Hospital, Los Angeles, California

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It has long been known (Ballenger, Elder and McDonald, 1932) that the cast distance and appearance of the external urinary stream provide useful information to the urologist to aid in the diagnosis of lower urinary tract obstruction. More recently (Zinner *et al.*, 1969*b*) high-speed photographs and cine-recordings have shown that the stream breaks into drops some 10 to 20 cm from the meatus and that the properties of these drops can be studied electro-optically by an instrument called the Urinary Drop Spectrometer (Zinner *et al.*, 1969; Zinner *et al.*, 1969*a*; Ritter, Zinner and Sterling, 1976). This instrument is being used clinically to screen and diagnose patients with various obstructive and neuromuscular disorders. In initial studies we have been able to correlate the patterns of drops within the stream with diseases such as benign prostatic hypertrophy, urethral stricture, obstructive ureterocele, meatal stenosis and similar conditions. Several forms of analysis are used as each provides a somewhat different view of the act of micturition and, more importantly, of the vesico-urethral system which cast the stream. One such analysis is called the time interval histogram (Zinner *et al.*, 1971). This analysis has also been

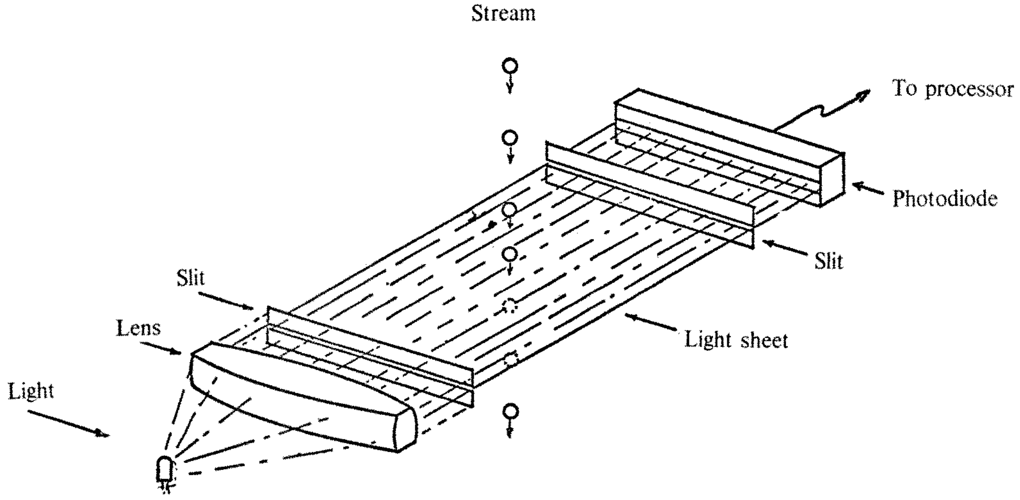

Fig. 1. Schematic representation of the transducer for the Urinary Drop Spectrometer.

used on brass models simulating the urethra and has been found to be highly sensitive to the location and degree of obstruction present (Ritter, Zinner and Sterling, 1974).

It is natural at this point to expect that much more information may be derived from the disrupted stream. By analogy with voice prints we would expect the information emitted to be susceptible to analysis by advanced techniques. This paper discusses some of the information we have found and the physical basis for expecting further information to be forthcoming.

General Information about the Stream

In the normal young adult male the flow rate varies from 15 to 30 ml/sec, when averaged over the entire voiding. In 2,000 voidings by 80 normal male subjects with the Urinary Drop Spectrometer (UDS) (Zinner *et al.*, 1969; Zinner *et al.*, 1969*a*; Ritter, Zinner and Sterling, 1976) we found that the average drop volume is 0·12 ml (excluding small "satellites" less than 0·02 ml) corresponding to a spherical drop of 0·61 cm diameter. Thus a flow rate of 20 ml/sec would empty a bladder with 250 ml in 12·5 sec, yielding an average of 2100 drops from which to gain statistical information.

A schematic diagram of the electro-optical transducer of the UDS is shown in Figure 1. As the drops fall through the light field, a photo-detector forms a series of electrical pulses which correspond to the series of drops which fall within the field. Examples of these pulses are shown in Figure 2. The fidelity with which the pulses represent the occlusion of light can be seen in Figure 3.

Calibration of the instrument is accomplished periodically by dropping steel balls of known diameter.

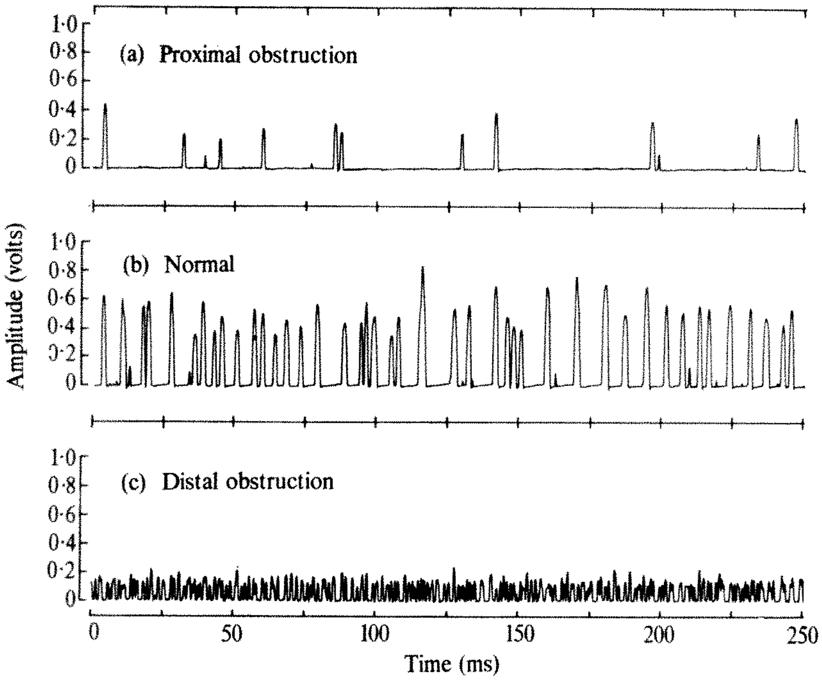

Fig. 2. Examples of pulses observed in clinical observations with the Urinary Drop Spectrometer. Data are from (*a*) a patient with a proximal obstruction (benign prostatic hypertrophy), (*b*) a healthy volunteer, and (*c*) a patient with a distal obstruction (meatal stenosis).

Stroboscopic studies of the live stream visually, and of photographs, show that the drops have a variety of sizes and shapes. Some are vibrating and some are rotating. Studies of high-speed movies show that there is a range of velocities. A two-slit version of the UDS (Zinner *et al.*, 1969; Zinner *et al.*, 1969*a*; Ritter *et al.*, 1976) enables the drop-by-drop measurement of velocity. A typical mean value for stream velocity at the point of breakup is about 200 cm/sec for normal male adults.

Classification of Expected Information

The reason for expecting information to be in the external stream is based on known properties of the break-up of liquid jets (Sterling, 1969; Ritter and Sterling, 1971). This results from the instability of a liquid jet in air which leads to the formation of discrete drops of fluid from the initially continuous stream. The details of the jet break-up are influenced by the microscopic fluid motions within the jet. These motions, in turn, are affected by geometric and elastic variations within the urethra. Thus the patterns imbedded in the sequence of drops are characteristic of urethral structure and function. In addition, abnormal urinations such as those caused by spastic sphincters or unusual bladder contractions lead to time sequences which are clearly distinguishable.

It is convenient and simple to speak of three regions of the urinary stream: (1) the internal, (2) the external before break-up, and (3) the external after break-up. Although it is an oversimplification, one can consider the information within the stream to reside essentially in a single form in each of these regions: in the vector velocity profile for region 1, in the surface shape and dynamics for region 2 and in the ensemble of drop dynamics for region 3. This is especially oversimplified for consideration of the internal stream within the complicated urethra where much of the information is imparted to the stream. Even though it is ultimately important, for simplicity we will not consider in detail the nature of these internal effects nor the retention and/or

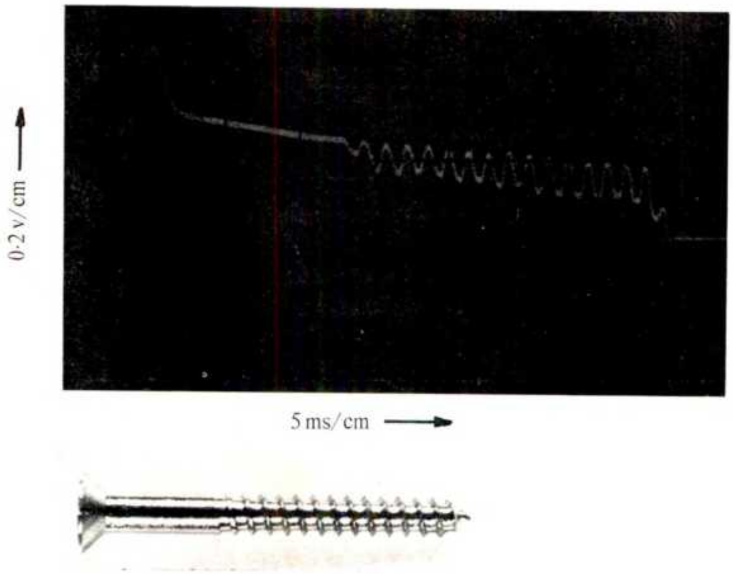

Fig. 3. Response of the Urinary Drop Spectrometer to a common wood screw dropped lengthwise through the light field.

modification of information as it passes towards the meatus. The ultimate properties of the data will have major features which survive this modification, as will be shown.

2 links connect the 3 regions. The first is the meatus. At this location, all possible influence by the particular urethra upon the otherwise standard stream has occurred. We can take up this link by noting that all this information resides in the form of the microscopic details of the fluid at the meatus. That is, each tiny element of the fluid has a speed and a direction which characterises what has happened to it in the urethra. The ensemble of this information for these particles in a plane (approximately) across the urethra at any given time contains the total intelligence retained, at that point, of what the urethra has contributed to the stream.

But since the flow is turbulent (Ritter, Zinner and Paquin, 1964) the minute particles have a variety of directions and speeds. Some of them started earlier than others, so in a sense, this plane contains a mixed "history" of the internal stream, *i.e.* in region 1. It is the existence of physical laws that require certain connections between successions of such planes, that permits us to assert that information is retained. Laminar, or streamline, flow would mix the information much less, but nevertheless, turbulent flow retains some of the features, as we have shown in mechanical jets (Lafrance *et al.*, 1974; Phinney, 1973).

The free unbroken stream, in region 2, undergoes certain simpler changes as a result of its freedom. For example, surface tension and inertia combine to determine the time it takes for the natural instability of the stream to cause its break-up into drops. They do this, very much dependent upon the microscopic state of the fluid at the meatus, particularly the shape and roughness of the fluid surface at that point. Hence, the fossa navicularis plays a substantial part in the transition from regions 1 to 2. Almost certainly, evolutionary development of this feature of the urethra is connected with hydrodynamical advantage.

The second link is at the point where the stream breaks into drops. It is not necessarily a constant distance from the urethra even in a single normal voiding. The linkage at this point has been studied by many, but only recently has a valid theory evolved for the detailed character of this break-up (Lafrance *et al.*, 1974; Lafrance, 1975). And this theory is strictly true only for laminar flow.

There is reason to believe that the turbulent eddies of "near turbulent flow"[1] can relax in region 2 where the wall drag is absent. These eddies form within the urethra by the strong drag of the wall on the fast-moving stream. In this pseudo-laminar regime the turbulences would have much less effect on the subsequent break-up than true turbulence. Phinney (1973) has shown this for the break-up distance and some of our work (Lafrance *et al.*, 1974) has shown it for the drop patterns.

In any case, the process of break-up is a major modification of the information in the stream. It is interesting that the break-up of a jet stream has been used as an acoustic amplifier (Boys, 1896) of periodic motions. This must imply a great sensitivity to certain periodic properties of the stream.

For example, could it be that the "tone" of the urethra causes minute vibrations of the wall which are imposed on the fluid and later modify the break-up? Studies of related vibrations in mechanical jets (Lafrance, 1975) imply this to some extent. Other studies (Lissenberg, 1974; Vliem, 1975) leave some question about it.

Once the stream is broken up, in region 3, the drops change spacing and shape as they progress, by virtue of their different velocities and vibrations. Ultimately, the viscosity will damp the vibrations, modifying the information further. The situation is tenable, however, and much can be done about understanding these region-3 modifications and the effect they have on extraction of certain types of information from the drops.

---

[1] Flow where the velocity is not much greater than it would be for laminar flow.

Physical Character of the Information in the Broken-up Stream

Once the stream has broken into drops the information can be sorted into the various structural and motional properties of the drops:

(*a*) Volumes or equivalent diameters;
(*b*) Shapes;
(*c*) Vibrations;
(*d*) Velocities;
(*e*) Rotations;
(*f*) Separations in time or space;
(*g*) Sequential relationships of any of these;
(*h*) Statistical relationships of any of these;
(*i*) Combinations of the above.

Of these properties, the volumes and separations are easiest to measure. In this paper we will concentrate on several aspects of the way they contain information.

Experimental Results and Interpretation

The average volume of drops in a urination can be determined by dividing the number of them into the total volume voided. To date this has been done only photographically and with the UDS. In Figure 4 we show a plot of average drop volume *vs.* total voiding volume for 3 normal subjects.

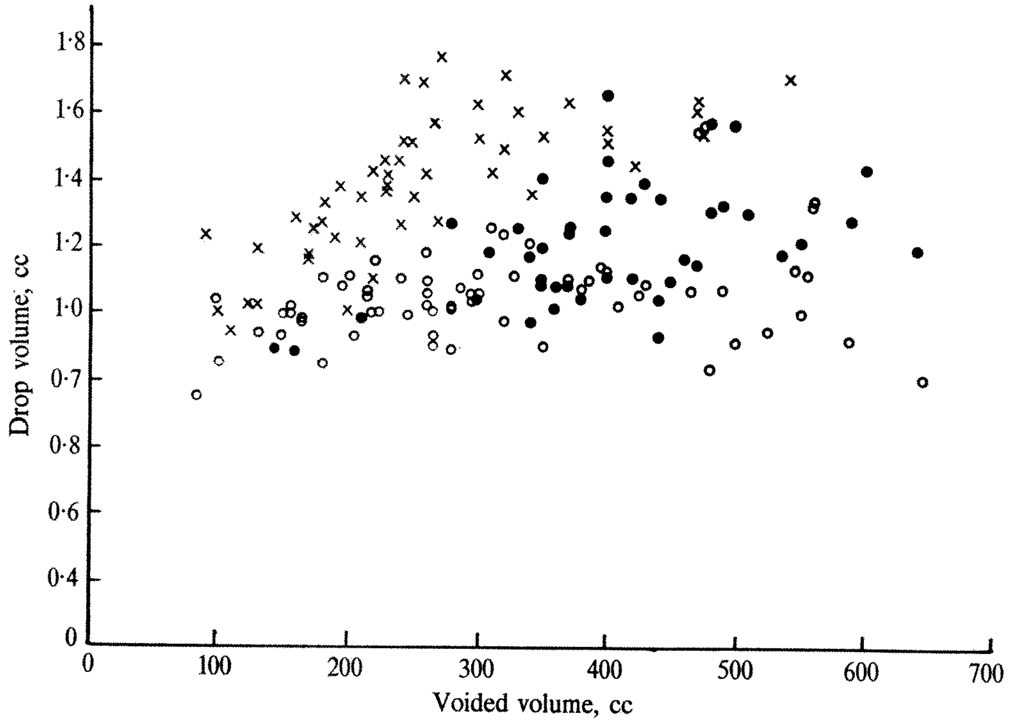

Fig. 4. Average drop volume for three normal subjects as a function of total voided volume.

3 points are clear: (1) each subject has some variation in his average drop size, (2) there is some difference between subjects, and (3) there is a decrease in the drop size at low voiding volume.

The primary interpretation of the average drop volume is in terms of meatus size. From the very old theory of Rayleigh (Rayleigh, 1879; Sterling, 1969; Ritter and Sterling, 1971) one can relate the average drop size to the meatal diameter:

$$D_{\text{drop}} = 1{\cdot}88\ d, \tag{1}$$

where D is the drop diameter and d is the canal diameter. This simple proportionality has been found in our laboratory to hold approximately, even though the meatus is very much elongated, provided an average radius is assumed for it.

A first observation is that the meatus is open less at the transition periods (Zinner *et al.*, 1969; Zinner *et al.*, 1971) at the onset and cessation of a voiding. Pulses from the UDS are definitely smaller at these periods; this partly explains why smaller voided volumes are associated with smaller average drop sizes. The transition periods are a larger part of the total voiding in these smaller voidings.

A second analysis is based on the frequency of drops. Even though the drop size may vary radically during one voiding, the number per second remains nearly constant at about 170. Thus, flow rate variations occur because the drop size is changing. Figure 5 illustrates this in a plot of flow rate throughout a voiding as compared with drop frequency during the voiding. We have found this to be typical even when the subject temporarily strained to increase pressure and flow rate or temporarily constricted the mid-urethra to decrease flow rate.

This indicates, therefore, that the normal meatus is highly compliant—that it responds in such

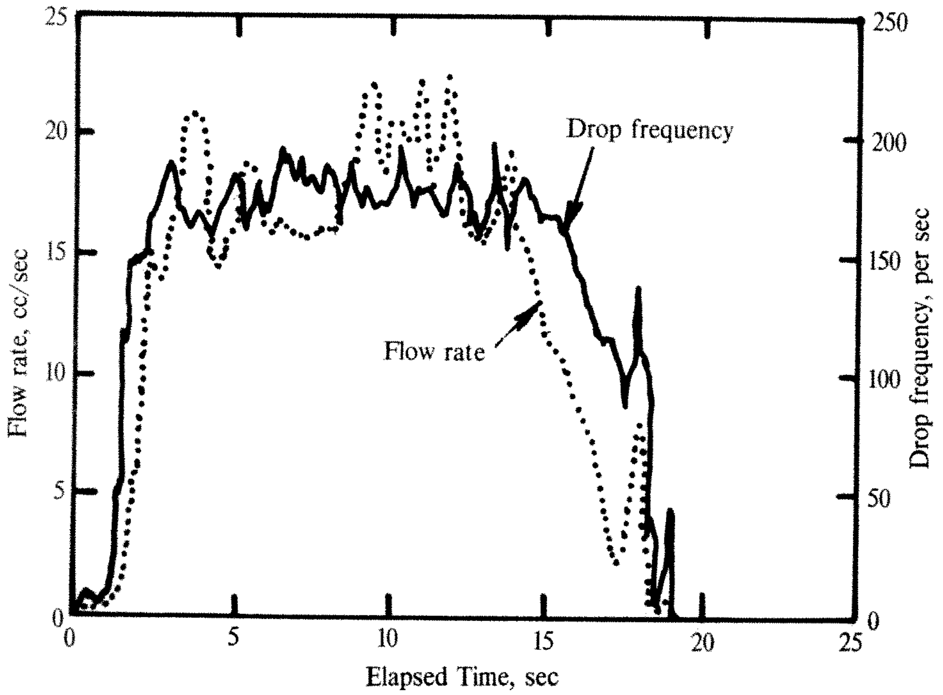

Fig. 5. Flow rate and drop frequency for a typical voiding of a normal subject.

a way as to keep the interval between drops nearly constant, even though the flow rate is changing. From the theory of Rayleigh (Sterling, 1969; Ritter and Sterling, 1971) the time interval between drops is calculated to be

$$t = \frac{\sqrt{2}\pi d,}{v} \tag{2}$$

where v is the velocity of the jet at the orifice. Thus, the effective diameter of the meatus is proportional to velocity. One pictures the sides of the meatus pressed outward proportionally to the stream velocity, which is controlled at more proximal locations.

Part of the usefulness of this information resides in its ability to discriminate stream changes occurring on a time scale of 0·1 sec and to discriminate truly between increases and decreases in drop frequency. An electronic instrument which analyses the UDS signal in this way is called a drop-frequency meter. In effect it gives a sequential graph of the number of drops passing each 0·1 sec.

As pointed out above, in the normal subject and most patients, the drop frequency is rather constant and drop size more sensitively represents urethral or bladder-pressure changes. The patient with meatal stenosis is an entirely different matter.

An electronic instrument which combines drop size (cubes the pulse height to duplicate drop volume) and frequency gives the flow rate. Thus the flow rate is given with response time of about 0·1 sec and with relative accuracy of better than 15%. In principle, and almost in practice, the accuracy is limited by the statistical fluctuations in the number of drops that pass a point in 0·1 sec.

A potentially important clinical consideration ensues from the fidelity of stream representation in such a measurement as compared with all flow-meters operating on standard principles, which must collect urine in some fashion to measure the flow rate. The collection process in effect destroys information on the time scale of 0·5 to 1·0 sec due to integration needed with such measurements. Furthermore, such instruments contribute artificial increases or decreases as the stream moves to and fro (Zinner *et al.*, 1971). Some problems created by such artifacts are in the discrimination between slow, smooth muscular activity such as bladder contraction, and faster

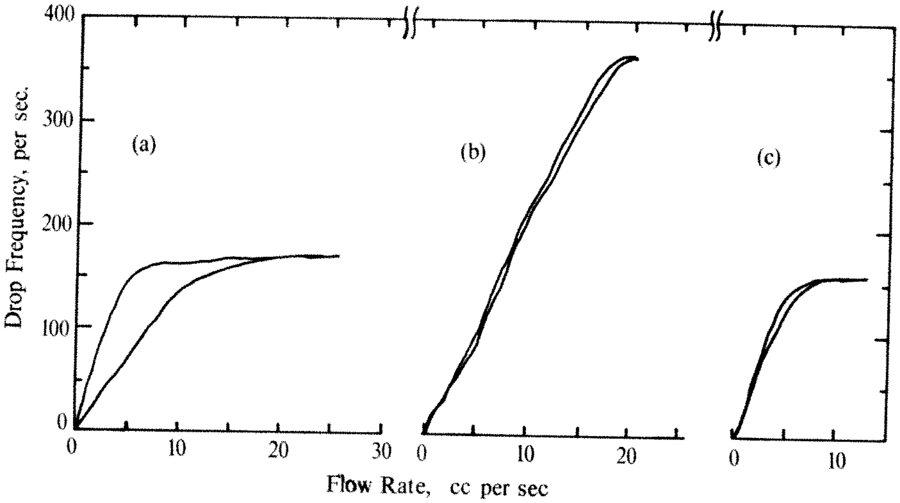

Fig. 6. Flow rate versus drop frequency for typical voidings: (*a*) normal subject, (*b*) patient with meatal stenosis, and (*c*) patient with moderate BPH.

activity such as spastic striated sphincter contraction or the mechanical effects of an obstructing bladder calculus or ureterocele.

In recent work we have found that a combination of the flow rate and drop-frequency rate can be used to determine meatal compliance (Sterling, 1976). On a 2-axis plot the flow rate is put into the x-axis and the drop frequency into the y-axis, as in Figure 6. As the voiding proceeds from the

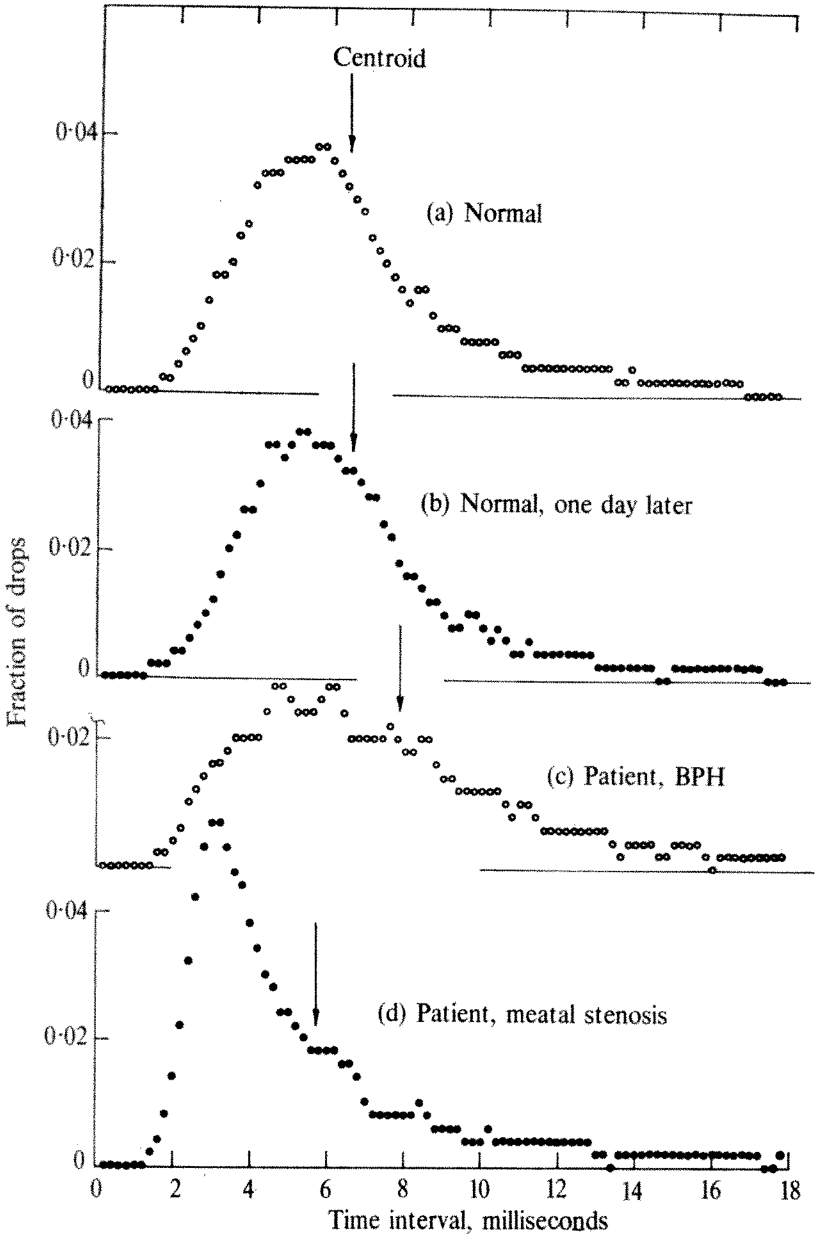

Fig. 7. Representative time interval distributions for 4 voidings: (*a*) normal subject, (*b*) same subject 1 day later, (*c*) patient with slight proximal obstruction, and (*d*) patient with moderate distal obstruction.

bladder-neck opening (transition stage) to the mid-period (plateau stage), the flow-frequency curve moves up over the bend as shown. In the bladder-neck closing transition stage, the flow-frequency curve moves back down.

The following interpretation of this information has been partly corroborated by observing patients with stenotic meatuses. For a normal person the transitional periods represent increasing pressure but with minimal change in diameter after an initial opening. The increasing flow rate comes about mainly from the increasing drop frequency. At the bend of the curve, the meatus starts opening in a manner proportional to velocity as indicated in the discussion following equation (2). The drop frequency stops increasing and the curve becomes horizontal. All flow-rate increase is caused by drop-size increase coming from increased meatal opening.

In a less compliant meatus, the horizontal curve is less distinct, and in patients with meatal stenosis it appears as in Figure 6b. Sometimes the drop frequency reaches 400 to 500 drops per sec, and the drops are smaller.

A patient with benign prostatic hypertrophy (BPH) often fails to develop either a high flow rate or high drop frequency. After a remedial operation, in successful cases, he develops a modified version of the normal pattern.

In a constantly flowing stream, the individual time intervals between drops must be related to the drop sizes. A logical extension of several of the above discussions would show how to treat such individual interval data.

A more statistical treatment of the drop intervals is gained from the time interval histogram or time interval distribution. During both transitional stages of voiding, the time intervals and drop sizes differ from the central or plateau stage. A "pure" histogram would include only the central stage. Practically, however, we have taken complete voidings and ignored these 1 to 2 sec contaminations. Patients with severe BPH never develop a stable central period.

Figure 7 shows several plots of these time interval histograms. The BPH patient shown exhibits one of the least broad distributions observed from this class of obstruction. Ranges of variation (Zinner *et al.*, 1971) and sensitivity to size of obstruction (Ritter *et al.*, 1974) have been reported.

Summary

The qualitative status of physical information contained in the stream of the male lower urinary tract is traced from the bladder to the broken-up external stream.

The progression of modifications of this information is discussed and it is argued that information remains in the drops.

Electro-optical measurements of the drops leads to pulses which can be analysed for various types of information content.

These confirm that there is potential clinical value in some aspects of the information.

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The Authors

R. C. Ritter, Professor, Department of Physics, University of Virginia.
A. M. Sterling, Associate Professor, Department of Chemical Engineering, Louisiana State University.
N. R. Zinner, Professor and Chairman, Division of Urology, Martin Luther King Hospital.

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Manometric and Electromyographic Assessment of Urethral Resistances in Children

PATRICK MEUNIER and PIERRE MOLLARD

From the Laboratoire d'Exploration Fonctionnelle Manometrique et Clinique Chirurgicale Pédiatrique, Hôpital Debrousse, Lyon, France

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Urethral obstruction is a common condition in the neurogenic bladders of childhood and in many other paediatric urological problems which require complete investigation of the bladder and its sphincters.

Cystometric evaluation of disturbances of micturition allows an orderly system of classification of neurological bladders which in children is better based on functional findings rather than on neurology (Pekarovic *et al.*, 1970; Upadhyaya, Singh and Parthasarathy, 1974; Meunier, Mollard and Habozit, 1975).

Electromyography of the perineal musculature has been used in detecting lower motor neurone lesions in patients with spina bifida (Chantraine, Lloyd and Swinyard, 1966). The combination of cystometry with EMG allows an understanding of pathophysiological relationships not observed with either technique used alone (Cardus, Quesada and Scott, 1963; Sundin and Petersén, 1975; Vereecken, Derluyn and Verduyn, 1975).

The urethral pressure profile provides additional information on the urethral closure pressure. This investigation is performed with a perfused side-opening catheter (Brown and Wickham, 1969).

Cystometry was performed in combination with EMG of the external anal sphincter in order to define vesico-sphincteric dysfunctions in children. A urethral pressure profile was recorded routinely after each examination.

Patients

84 children were examined, their ages ranging from 5 months to 17 years (mean age = 7·2 years). There were 46 girls (55 %) and 38 boys (45 %). The children were divided into 3 groups according to their urological dysfunctions.

The first group consisted of 57 children (68 % of the total number) with neurogenic bladder dysfunction. In this group were 31 girls and 26 boys (mean age = 6·8 years). 45 of the patients suffered from myelomeningocele ("spina bifida" patients in Tables of Results). The 12 others had neuropathic bladders for other reasons ("diverse neuropathies" in Tables of Results): 3 post-traumatic paraplegics, 3 sympathoblastomas, 3 sacral tumours, 2 sacral agenesis and 1 haemato-myelitis.

The second group included 14 children (16 % of the total number) with diverse urological problems ("Diverse Uropathies" in the Tables of Results). They were aged between 6 months and 14 years (mean age = 6·4 years) and suffered from the following disorders: 8 ureteric malformations, 3 urinary fistulae due to imperforate anus and 3 urethral malformations.

The third group was made up of 13 enuretic children, aged 4 to 15 years (mean age = 8·4 years) including 8 girls and 5 boys.

For ethical reasons this examination was not performed on normal children. Our conception of "normal" was based on enuretic children, whose clinical, radiological, cystometric and EMG findings did not demonstrate intravesical obstruction or neurological disorder.

All children of the present series underwent this examination before undergoing medical or surgical treatment for urological disease.

Methods

1. *Cystomanometry*

To avoid any increase in urethral resistance and probably changes in bladder pressure, the technique of suprapubic puncture, rather than urethral catheterisation, was chosen.

A catheter (Bard—A round needle 14G × 15½) was inserted suprapubically under a light anaesthesia with halothane. This catheter was used for both pressure measurement and bladder filling with saline (framycetine sulphate added: 10 mg at 0·5 l) at a flow rate of 3 to 6 ml min^{-1}. The examination was performed 2 hours after wakening, with the child in the supine position. The rectal pressure (measured with a 10F side-opening perfused catheter: flow rate = 0·24 ml min^{-1}) and the pneumogram were also monitored, in order to eliminate all extraneous factors affecting the bladder pressure recording. Data were transmitted via three electromanometers (Hewlett-Packard mod. 1280 c), amplified (H.P.8805 B) and recorded on a Hewlett-Packard thermal-tip recorder (mod. 7758 A). With the exception of restless infants, instant pressures, rather than average pressures, were recorded.

Pressure recordings were analysed for bladder tone, activity and contractility.

(I) *Bladder tone* (a purely myogenic property) is defined as the adaptability of the detrusor during the filling phase. The bladders were found to be normotonic (5 to 25 cm H_2O) or hypertonic (over 25 cm H_2O). (II) *Activity* is defined as bladder contraction frequency. Due to the wide range of ages, "*normal activity*" varied from 100 to 350 ml of vesical capacity. *Hyperactivity* is defined as bladders in which contractions appearing at smaller capacities. *Inactivity* is defined as bladders in which no contractions were ever observed. (III) *Contractility* is defined as the amplitude of contractions: normo- (40 to 80 cm H_2O), hypo- (under 40 cm H_2O) or hyper-contractile (over 80 cm H_2O). Activity combined with contractility provided bladder motility patterns.

2. *Anal Electromyography*

EMG of the external anal sphincter was performed during 54 examinations.

Two monopolar Pt electrodes (diameter = 0·35 mm), spaced 2 to 5 mm apart, were inserted on the anal margin. Gross (bipolar leads) and direct EMG were monitored with a Hewlett-Packard amplifier (mod. 8511 A) and a thermal-tip recorder. EMG activity during micturition or manual bladder expression (Crédé manoeuvre) was rated according to the following patterns: decreasing (normal), increasing, remaining basal, practically nil. In the 2 latter cases, EMG activity was not modified during micturition or on manual expression.

3. *Urethral Pressure Profile*

This was performed after each examination with a 8F PVC catheter, having one side-opening (2 mm × 1 mm) perfused with saline at 4·4 ml min^{-1}. A manual pull-through technique was used at a speed of approximately 20 cm min^{-1}. Urethral maximal resistance was calculated by subtracting the empty bladder pressure value from the maximal pressure observed in the urethra.

4. *Other Parameters*

(i) *Volume of filling* and *loss of urine* (when observed) were marked in the margin of recordings.

(ii) Voiding was noted to be *spontaneous* (loss of micturition), or *provoked* (by manual expression). *Urine streams* were described by one of three terms: dribbling, weak stream, or strong stream.

(iii) *Residual urine* (after micturition or manual expression) was measured and expressed in percentage.

5. *Urethral Resistances*

Urethral resistances were assessed with reference to the different parameters defined above. Four functional groups were established:

(i) The *non-resistant* group included normotonic and inactive bladders. Maximal urethral

Tables of Results—In these tables, the following abbreviations are used: S.B. for spina bifida, D.N. for diverse neuropathies, D.U. for diverse uropathies, and E. for enuretics.

Table I

Bladder Tone

Tone	Total number	S.B.	D.N.	D.U.	E.
Normotonic	71	36	9	13	13
Hypertonic	13	9	3	1	–

Table II

Bladder Activity

Activity	Total number	S.B.	D.N.	D.U.	E.
Not active	22	14	6	2	–
Normoactive	28	3	1	11	13
Hyperactive	34	28	5	1	–

Table III

Bladder Contractility

Contractility	Total number	S.B.	D.N.	D.U.	E.
Not contractile	22	14	6	2	–
Hypocontractile	28	26	1	1	–
Normocontractile	28	2	2	11	13
Hypercontractile	6	3	3	–	–

Table IV

Bladder Global Motility Patterns

Motility	Total number	S.B.	D.N.	D.U.	E.
Normoactive, hypocontractile	1	–	1	–	–
Normoactive, normocontractile	26	2	–	11	13
Normoactive, hypercontractile	1	1	–	–	–
Hyperactive, normocontractile	2	–	2	–	–
Hyperactive, hypercontractile	5	2	3	–	–
Hyperactive, hypocontractile	27	26	–	1	–
Not active, not contractile	22	14	6	2	–

Table V

EMG Activity during Micturition or Crédé (54 Examinations)

EMG pattern	Total number	S.B.	D.N.	D.U.	E.
Practically null	15	13	1	1	–
Increasing under Crédé	14	9	4	1	–
Remaining basal	8	5	2	1	–
Increasing under micturition	6	1	4	1	–
Decreasing under micturition	11	–	–	4	7

resistance was found to be between 0 and 5 cm H_2O. From the onset, urethral loss equalled bladder inflow. Residue was absent.

(ii) The *hyporesistant* group, with normotonic bladder and various motility patterns was found when incontinence appeared only after a threshold capacity was reached. Maximal urethral resistance was found to be between 7 and 35 cm H_2O. Residue was absent or small after manual expression.

(iii) The *normoresistant* group with normotonic, active and always normocontractile detrusors included bladders with a urethral maximal resistance theoretically elevated. There was no urine loss, except during micturition, and no residual urine.

(iv) The *hyperresistant* group, was associated theoretically with bladder hypertonia and various motility patterns. Urethral resistance should be high. A large residue was found after micturition or manual expression.

Results

1. *Detrusor* (Tables I-IV)

Tone was normal in the large majority of cases (Figs. 1-4). Not surprisingly, normal bladder activity and contractility (Fig. 1) was observed in all enuretic children and in 11 diverse uropathies (79% of cases). The persistance of some motility was not infrequent in neurogenic bladders (65% of the cases) and, especially, in spina bifida (69% of the cases). In patients with myelomeningocele, when the bladder was still active, the most frequent motility pattern observed (84% of the cases)

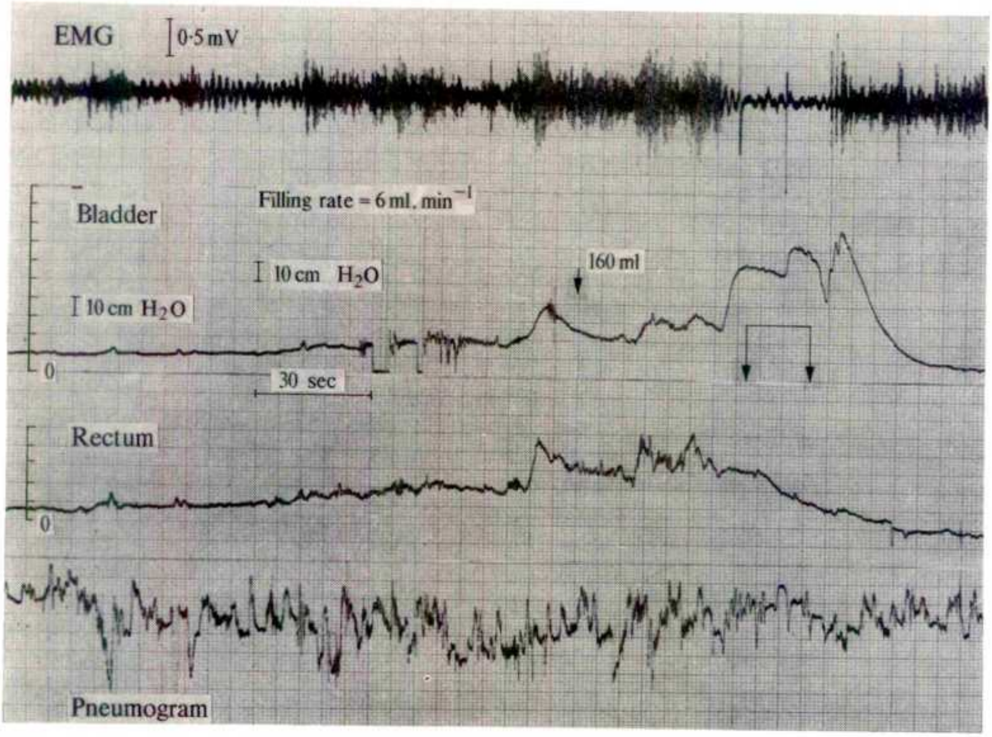

Fig. 1. Normoresistant bladder outlet (Enuretic patient). Detrusor was normotonic, normoactive, and normocontractile. EMG decreased during micturition (between arrows). Urine stream was strong. A postcontraction was observed after micturition. No strain aided voiding, but as shown on pneumogram, movement and irregular respiration preceded micturition. Residual urine was absent. Maximal urethral resistance was 60 cm H_2O.

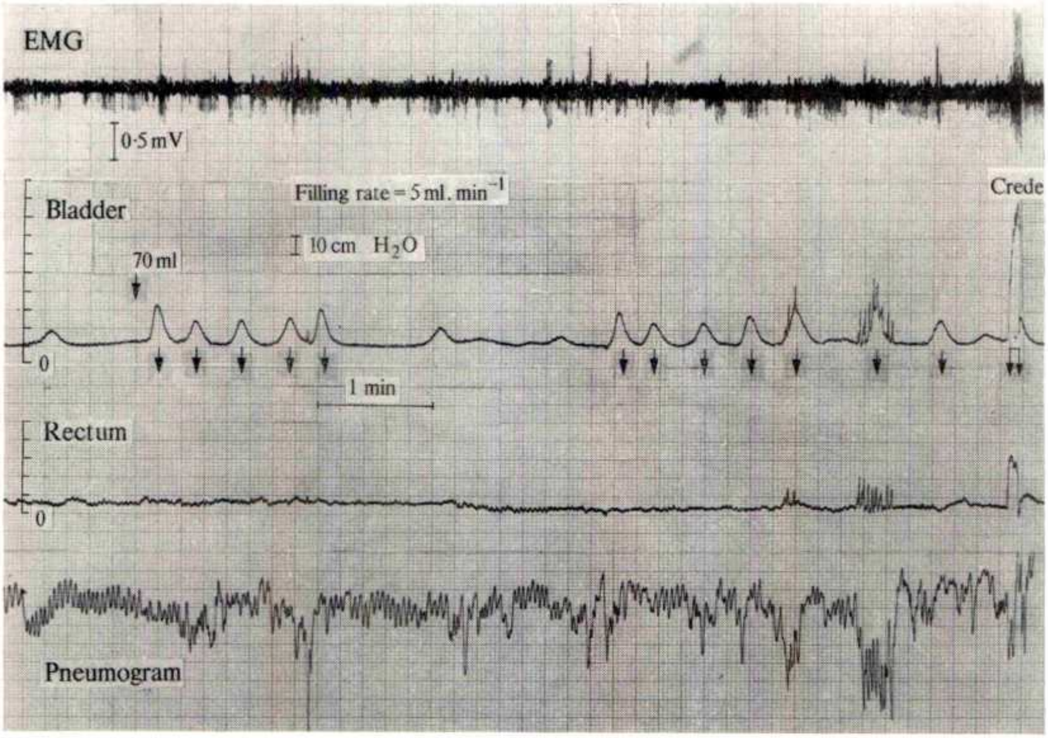

Fig. 2. Hyperresistant bladder outlet (Spina bifida child). Detrusor was normotonic, hyperactive and hypocontractile. Anal EMG increased during Crédé, which produced a strong stream with a small residue (10%). Above 70 ml of filling, dribbling (arrows) appeared induced by each light contraction. Residue was 10% and maximal urethral resistance was 10 cm H_2O.

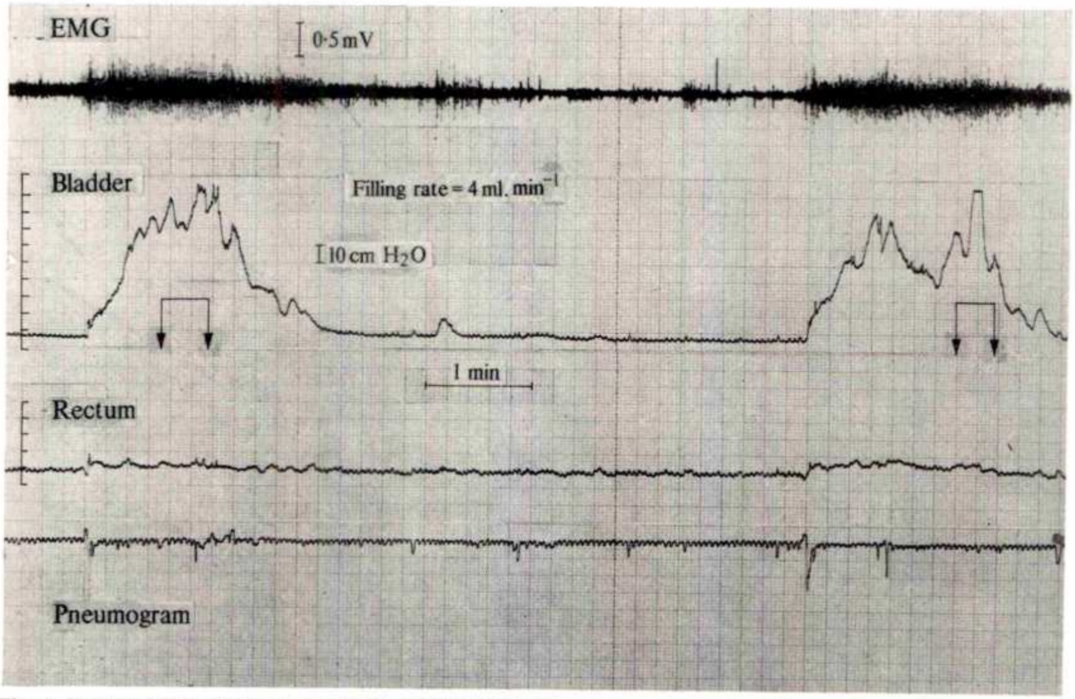

Fig. 3. Hyperresistant bladder outlet (Spina bifida child). Detrusor was normotonic, hyperactive and hypercontractile. Incontinence was due to uninhibited reflex contractions (voiding periods between arrows). There was asynchrony between bladder and sphincter, because EMG activity greatly increased during voidings (with strong streams). Post-voiding residue was 50% and maximal urethral resistance was 60 cm H_2O.

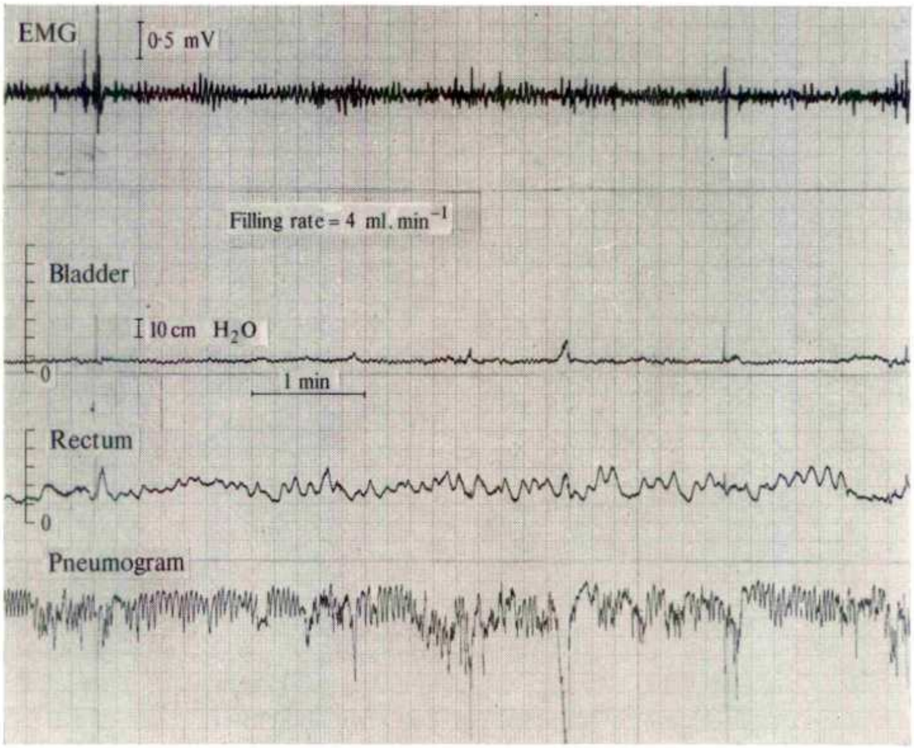

Fig. 4. Non-resistant bladder outlet (Spina bifida patient). Detrusor was normotonic and inactive. Anal EMG recording practically null, shows only isolated spikes on a parasited base-line. From the onset, dribbling equalled inflow. Residue and maximal urethral resistance were null.

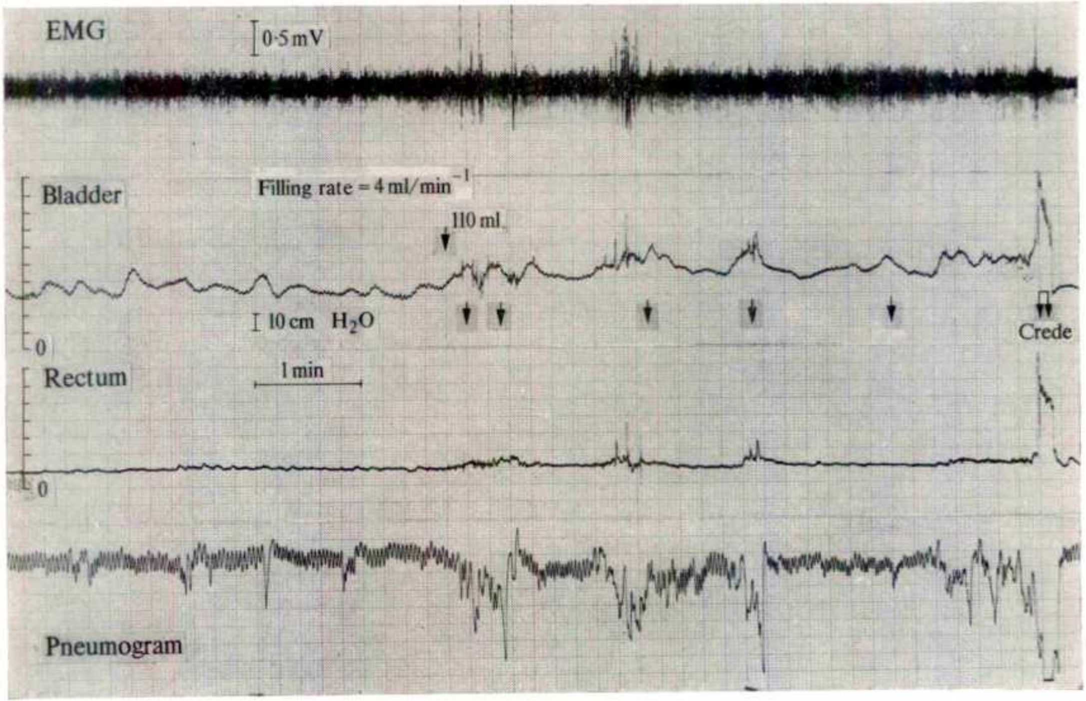

Fig. 5. Hyperresistant bladder outlet (Spina bifida patient). Detrusor was hypertonic, hyperactive and hypocontractile. EMG remained basal during entire examination and Crédé manoeuvre. The "spastic" contraction of the external sphincter may be considered as a proof of a permanent functional obstruction. Dribbling (arrows) appeared above 110 ml. Residue was 66%, and maximal urethral resistance was 50 cm H_2O.

was hyperactivity with hypocontractility (Figs. 2 and 5). Normal motility patterns were rarely observed in spina bifida (4% of the cases) and never observed in diverse neuropathies. Hypercontractility (Fig. 3) was noted only in the hyperresistant group (30% of the cases), In those children with diverse uropathies and presenting "neuropathic" bladder pressure recordings (3 cases), it is likely that only the lack of urethral resistance does not allow the development of normal bladder motility.

2. *Anal EMG during Micturition*

Table V shows the 5 typical patterns observed on 54 recordings:

(i) EMG activity was almost absent (Fig. 4) in 15 cases, including 14 neurogenic bladders. The only case among the diverse uropathies in which a lack of anal EMG activity was observed concerned an imperforate anus.

(ii) An increase of anal EMG activity during the manual expression manoeuvre (Fig. 2) was obtained in 14 examinations. Such a reflex contraction could prevent adequate bladder expression. Although the residual urine was small (from 0 to 23% with a mean of 2·14%) in 7 cases, it was much greater (from 30 to 80% with a mean of 50·15%) in 7 others.

(iii) EMG activity remained basal during the complete investigation (Fig. 5) in 8 cases, *i.e.* there was a total absence of synergy between the detrusor and the striated musculature.

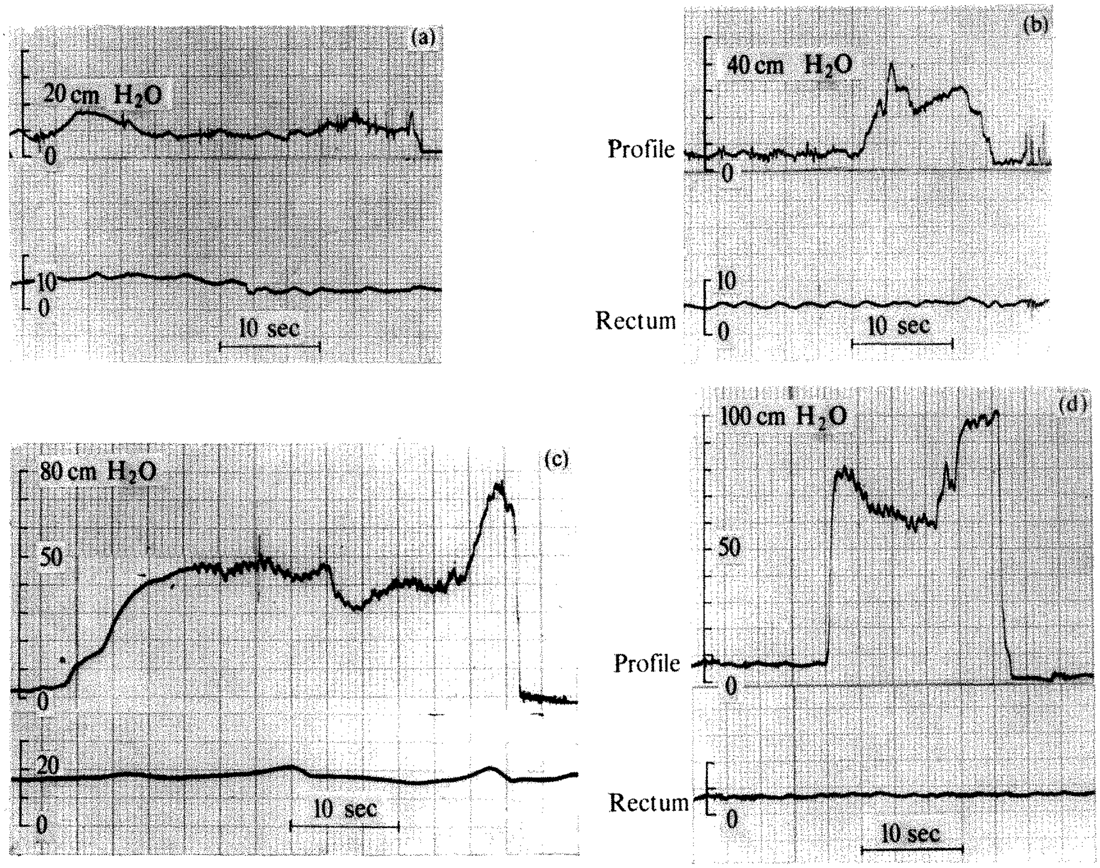

Fig. 6. Typical urethral pressure profiles. Pressure in the rectum was recorded, in order to be certain that the urethral profile was not modified with strain. In A, non-resistant profile (girl); in B, hyporesistant profile (girl); in C, hyperresistant profile (boy); and in D, normoresistant profile (enuretic girl).

(iv) Anal EMG activity increased during micturition (Fig. 3) in 6 examinations. This pattern indicated bladder and sphincter asynergy. In 5 cases out of 6, the residue was large (between 40 and 72% with a mean of 51·6%).

(v) EMG activity decreased during micturition notably in the 7 enuretic children in whom it was measured. This inhibition is normal. This pattern was not found in any child suffering from a neuropathic bladder. Residual urine in this group was between 0 and 17% (mean residue 3·85%).

3. *Urethral Pressure Profile*

Urethral pressure profile was performed in all 84 examinations. Figure 6 shows typical pressure profiles. A wide range of values in maximal resistance was observed, ranging from 0 to 108 cm H_2O. Correlation between residue and urethral maximal resistance (Fig. 7) were calculated for non-, hypo- and hyperresistant groups. The global correlation coefficient for these 3 groups was found to be 0·77. This coefficient was found to be 0·35 for the normoresistant group.

4. *Residual Urine*

Values (expressed in per cent) were found to be between 0 and 80%.

5. *Aspects of Urine Stream and Continence or Incontinence*

24 children were continent: 16 presented a strong stream, and the other 8, a weak stream.

60 children were incontinent. In 8 cases, incontinence appeared from the onset of filling, the

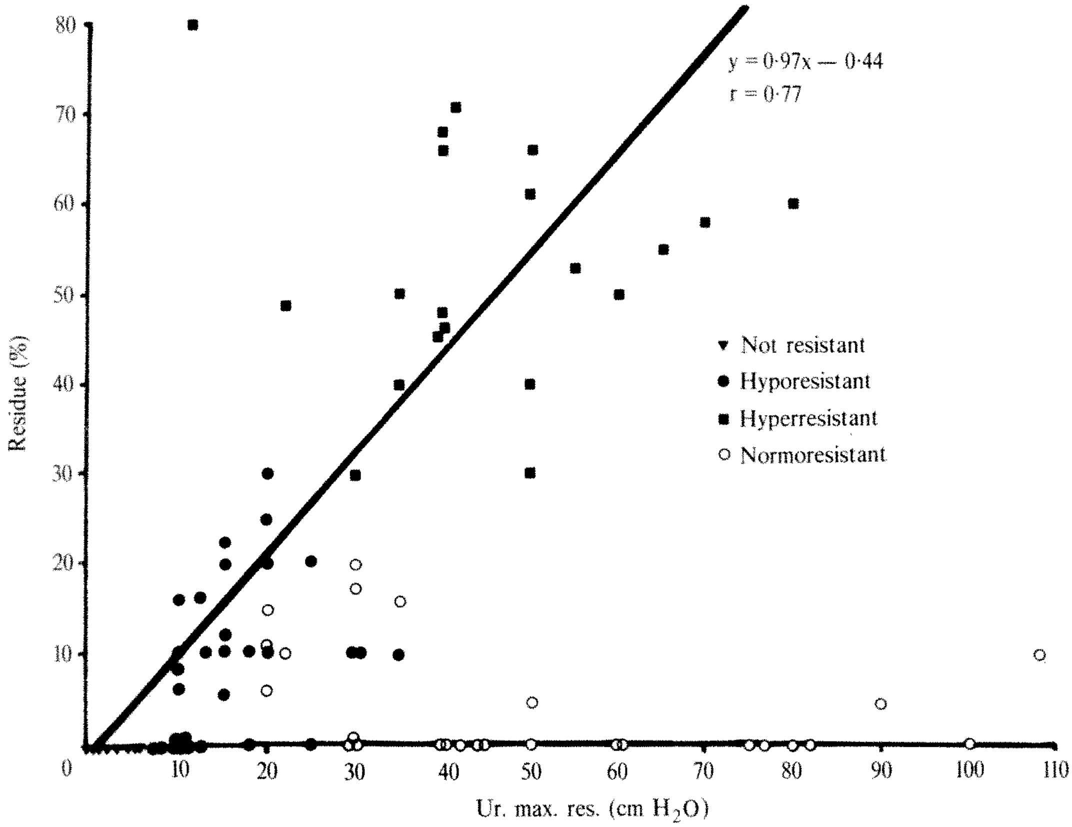

Fig. 7. Correlation between residue and maximal urethral resistance. Calculated for the non-, hypo- and hyperresistant group the coefficient was 0·77. For the normoresistant group no correlation was found ($r = 0{\cdot}35$).

Table VI

Urethral Resistances

Resistances	Total number	Sex M	Sex F	S.B.	D.N.	D.U.	E.
Non-resistant	8	–	8	6	1	1	–
Hyporesistant	30	15	15	25	4	1	–
Hyperresistant	20	12	8	12	6	2	–
Normoresistant	26	11	15	2	1	10	13

outflow being equal to the inflow. In 42 cases, incontinence with dribbling appeared after a threshold capacity (between 25 and 280 ml with a mean of 121·87 ml) was reached. In the latter children, manual expression induced a strong stream in 34 cases and only a weak one in 8 cases. In 10 children, incontinence was due to uninhibited reflex micturition. The stream was weak in 6 and strong in 4 of these children.

6. *Urethral Resistance* (Table VI)

(i) *The non-resistant group* (Fig. 4) included 8 children (all girls). Bladder tone was normal at all the times, and activity was always absent. Anal EMG activity during 5 examinations was practically absent 4 times (group of neurogenic bladders) and was remaining continuously basal 1 time (group of diverse uropathies). In this non-resistant group, dribbling equalled inflow from the onset. Maximal urethral resistance was found to be between 0 and 5 cm H_2O (mean = 2·5 cm H_2O). Residual urine was absent.

(ii) *The hyporesistant group* included 30 children, with a large majority of myelomeningocele patients (83% of the cases). Bladder tone was normal at all times. Inactivity was observed on 12 occasions and hyperactivity with hypocontractility (Fig. 2) was noted in 18 other cases. Anal EMG activity was about absent in 9 cases but increased during manual expression in 7 children (Fig. 2), and it remained basal, in spite of the expression in 5 patients. All children in this hyporesistant group were incontinent. Dribbling appeared when a threshold capacity (25 to 280 ml with a mean of 120 ml) was reached. During manual expression the stream was strong at all times. Urethral maximal resistance was found to be between 7 and 35 cm H_2O (mean = 16·6 cm H_2O). Residue after manual expression was found to be between 0 and 30% (mean value = 9·3%).

(iii) *The hyperresistant group* (20 cases). 13 were hypertonic (Fig. 5) and 7 were normotonic (Fig. 3). Various patterns of motility were observed (Table IV), with, most often (45%), hyperactivity and hypocontractility (Fig. 5). Hyperactivity with hypercontractility (Fig. 3) was observed in 25% of cases. Anal EMG activity, recorded 13 times, was increased during micturition (Fig. 3) or manual expression in 12 cases, and remained basal (Fig. 5) in 1 case. Incontinence was observed in 19 cases. The 1 continent patient had urethral valves. Incontinence with dribbling over the capacity threshold (90 to 240 ml with a mean of 133·75 ml) was observed in 7 children, and incontinence with uninhibited reflex micturitions was found in 7 children. Urethral maximal resistance was found to be between 12 and 80 cm H_2O (mean = 45·3 cm H_2O). Residue after manual expression or micturition was found to be between 30 and 80%, with a mean of 53·1%.

(iv) *The normoresistant group* (26 cases) included, not surprisingly, all 13 enuretic children and 10 diverse uropathies. Bladder tone was normal in all children. Hyperactivity was observed once (paraplegia). Anal EMG activity during micturition (15 examinations) was increased in 1 patient and decreased in 11 (Fig. 1). It was almost absent in 2 cases and remained basal on 1 occasion. In 3 children (neurological bladders), incontinence due to uninhibited reflex micturitions was observed. Continence was observed in all other 23 cases. The urinary stream was weak in 8 examinations and strong in all other cases. Maximal urethral resistance was found to be between 20 and 108 cm H_2O (mean = 50·26 cm H_2O), and residue found to be between 0 and 20% (mean value = 4·46%).

Discussion

Progressive renal damage is the most important complication in children with neurogenic bladders (Thomas, Zachary and Lister, 1974; Cass, 1976). The main point worthy of discussion is, therefore, the assessment of urethral resistance by the method described above.

King, Mellens and White (1965) and Pekarovic *et al.* (1970) found that cystometry provided a useful assessment of bladder resistance in children. However, Donohue and Leadbetter (1964) were of the opinion that voiding pressure studies (250 cystometrograms performed) were of little practical value in the assessment of bladder outlet obstruction. In the series of examinations described above, bladder tone was normal in 7 cases with raised resistance and various motility patterns were shown in this group. Although hypertonia and hypercontractility are found only in the presence of increased resistance the absence of these findings does not prove that urethral obstruction is absent. Cystometry alone is, therefore, useful but inadequate in the assessment of bladder outlet obstruction.

Anal EMG recording alone cannot elucidate the problem of micturition disturbances. However, when combined with cystomanometry, diagnosis becomes more accurate (Cardus *et al.*, 1963). The choice of the external anal sphincter rather than of the urethral sphincter or pelvic floor for EMG studies is debatable. Although Chantraine *et al.* (1966) using spina bifida patients, and Sundin and Petersén (1975) investigating normal adults presented evidence that the functional status of the external anal sphincter parallels that of the urethral sphincter, a recent study by Vereecken *et al.* (1975) concerning EMG of the urethral sphincter, anal sphincter and pelvic floor, showed differences in response of these muscles in the presence of disease. In our series, 9 out of 54 recordings (16%) of anal EMG activity did not correlate with other findings. In 1 case of imperforate anus (above the levator ani), EMG activity was absent, although other parameters, and in particular urinary continence, were normal. In such cases, a urethral EMG would certainly provide better results. EMG activity increased during micturition in 1 paraplegic patient, but the residue was only 15%. Anal EMG activity was increased by manual expression in 7 spina bifida children, although mean residue was only 9·14%. Certain erroneous interpretations are thus possible with anal EMG studies. However, in children (sometimes younger than 1 year), urethral EMG is difficult to perform and one is never certain that the electrodes are properly placed in the sphincter. Our own experience of pelvic floor EMG, like that of Sundin and Petersén (1975), shows that the activity of this muscle does not parallel that of the anal urethral sphincters very accurately. Anal EMG, which is very easy to perform, offers, when combined with cystometry, a useful assessment of detrusor and sphincter synergy or asynergy.

Contrary to the findings of Upadhyaya *et a.l* (1974), the urinary stream was found to be unreliable because all 3 variants were observed in the hyperresistant group.

The urethral pressure profile, using the simple technique described above, is a measurement which on its own is certainly not very accurate. A wide range of values for urethral maximal resistance was found in normo- and hyperresistant groups, the mean values for these 2 groups being 50·26 and 45·3 cm H_2O, respectively. These values are not significantly different. Errors are due to a single aperture manual pull-through, and lack of an X-Y recorder. The urethral pressure profile, as recorded by Harrison and Constable (1970), Edwards and Malvern (1974) and others, is much more precise and reproducible. According to these authors, this investigation is in itself diagnostic. In our studies, the urethral pressure profile is only an additional measurement never to be considered in isolation. For example, correlation of maximal resistance with residue (Fig. 7) gave a significant correlation coefficient ($r = 0{\cdot}77$) for non-, hypo-, hyperresistant groups, while, not surprisingly, correlation is absent ($r = 0{\cdot}35$) for the normoresistant group. Although easily obtained, the maximal resistance value provides, nevertheless, an interesting additional parameter.

Residual urine is certainly the most reliable single measurement. Mean values obtained in the non-, hypo-, hyper- and normoresistant groups were, respectively: 0, 9·3, 53·1 and 4·46%. Residue in itself is of great clinical interest, but not diagnostic on its own.

It therefore seems evident that each particular parameter, isolated from the others, is insufficient for accurate assessment of bladder outlet resistance. All observations must be considered together and compared with radiological findings (especially a voiding cystourethrogram) and urinary infection studies. Out of the 84 examinations mentioned above, a close correlation between results was found in 83 cases. In 1 case (spina bifida), although manometric and EMG findings were of the hyporesistant type, an obstruction at the urethral sphincter was clearly observed on the voiding cystourethrogram, and urinary infection was found. In this case the residue value was 25% after manual expression, a very high value for the hyporesistant group. In contrast to this latter case, in the non-, hypo- and normoresistant groups no obstruction was observed on the voiding cystourethrogram, and infection was only occasionally present. Intravesical obstruction and urinary infection were constantly found it the hyperresistant group.

Cystomanometry combined with anal EMG has the great advantage over radiology alone in providing a dynamic assessment of bladder and sphincter function. This examination allows an assessment of micturition parameters and permits follow-up studies which are of importance in deciding management of the patient. This will be the subject of a future paper.

Summary

In an attempt to define urethral resistances in children, 84 cystometries were performed, combined with an anal EMG in 54 cases. The urethral pressure profile was measured in each patient.

The following parameters were studied: bladder tone, activity and contractility; micturition EMG; maximal urethral pressure; aspects of the urine stream; and residual urine.

It was found that each parameter considered alone is insufficient for assessment of bladder outlet obstruction. Only the complete investigation proved to be highly reliable as a complement to radiological findings, and allowed a dynamic assessment of bladder and sphincter functions.

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Prostatectomy with a No-catheter Technique

G. HUBMER, H. LIPSKY, P. PETRITSCH and F. EPPICH
Department of Urology, University of Graz, Austria

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In spite of the increasing role of transurethral resection (TUR) in the management of benign prostatic hypertrophy (BPH), open surgery has kept its place for the larger prostate and where there is co-existing bladder disease. Open prostatectomy does not always remain a sterile procedure because of pre- and postoperative infection of the bladder mainly caused by the use of the catheter.

Every effort should also be made to avoid postoperative infection.

We started a no-catheter transvesical prostatectomy in which Redi-Vac suction was used for postoperative drainage of the bladder (Bergmann and Hubmer, 1968; Hubmer, 1970). The experience with this technique has now been reviewed.

Method

A lower midline incision is performed under general or epidural anaesthesia. The bladder is opened, the adenoma exposed and the bladder mucosa over the adenoma incised with a cautery. The adenoma is enucleated digitally and the prostatic arteries and other bleeding vessels controlled by sutures placed especially at 5 and 7 o'clock position. 2 catgut sutures are left uncut. The bladder neck remains widely open and a wedge is excised; only extremely

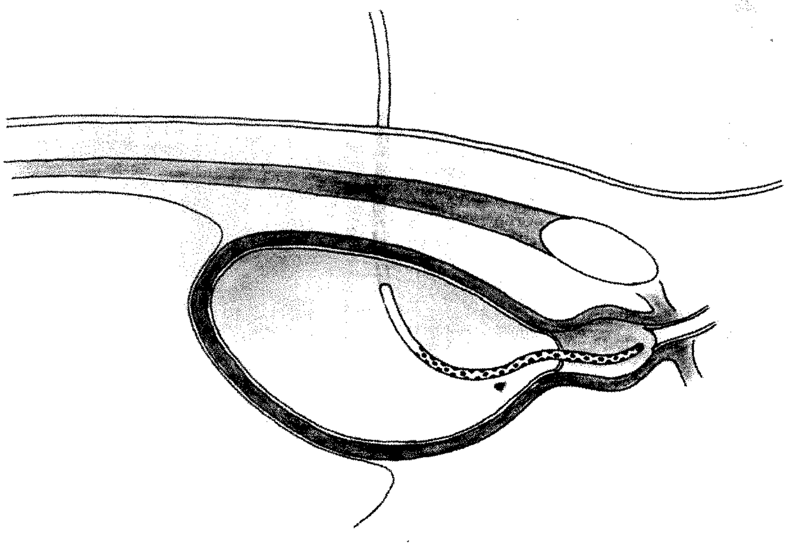

Fig. 1. Position of Redi-Vac drainage after prostatectomy.

wide bladder necks were narrowed by anterior sutures. 2 Redi-Vac drains are inserted into the prostatic cavity across the bladder and fixed with loosely tied knots of the 2 long catgut sutures, so that $\frac{2}{3}$ of the perforations of the drains are in the bladder and $\frac{1}{3}$ in the prostatic cavity (Fig. 1). The drains are brought through the bladder wall with forceps on each side of the cystotomy and through the abdominal wall using the spike introducer. The bladder is closed with a prevesical drain and the Redi-Vac drains are connected to their bottles and suction is started as soon as the wound is closed. Diuresis is stimulated by intravenous infusion and, if there is bleeding, by frusemide or mannitol. Vasectomy was performed in the earlier patients, but has not been done in recent patients.

Postoperative care has been simple. Full or badly working bottles are changed. During the first 24 hours approximately 6 bottles are necessary. Later 2-4 bottles a day cope with the drainage. Obstruction of the system with blood clots is rare but may happen within the first hours. The Redi-Vac drains can be washed easily with sterile saline solution. A good diuresis at that period will generally avoid this complication. The first Redi-Vac drain is removed on the 3rd day, the second on the 6th-7th day. If the drains are blocked and the patient is capable of passing his urine without difficulty and there is no suprapubic leak, then the drains may be removed earlier. The silicone drain in the space of Retzius is removed on the 3rd postoperative day. Some patients may pass urine per urethram although the drainage system works sufficiently, but this occurs mainly due to detrusor spasms. If the patient suffers from bladder spasms a spasmolytic drug is given. If there is severe postoperative bleeding a balloon catheter is inserted transurethrally, the bladder washed out and the catheter left in position till the bleeding has stopped. Catheterisation is not difficult despite the presence of the Redi-Vac drains in the prostatic cavity. Further drainage of the bladder continues by Redi-Vac suction. The patients are mobilised and start walking on the first postoperative day.

Results

Since 1967 we have operated on 350 patients with this no-catheter method. The functional results have been excellent. Only 3 patients have developed a moderate stricture of the bladder neck, and in 1 a TUR was necessary to improve his stream. The mortality was 2% (7 patients). All but 1 died from pulmonary emboli.

Urinary infection. Antibiotics and chemotherapeutic agents were administered in 265 patients for various reasons, the most frequent being urinary infection and broncho-pneumonia. 85 patients came to operation with sterile urine and these patients were not treated with antibiotics. From this group only 10 developed a significant urinary infection after operation (Table I): in 4, this was due to *Pseudomonas pyocyaneus*, in 2 to proteus species, in 3 to *E. coli* and in one case to *K. aerogenes*. There was a mixed infection in 4 patients and in 6 a single infection. There were 14 patients in the whole series who showed persistent urinary infection.

Table I

Chemotherapy and Urinary Infection in 350 Patients

With chemotherapy	265	
Without chemotherapy	85	
No postoperative bacteriuria		48 (57%)
Significant bacteriuria		10 (11%)
Not checked (asymptomatic)		27 (32%)

Table II

Complications in 350 Cases of Catheterless Prostatectomy

Mortality	7 (2%)
Severe postoperative haemorrhage (controlled by catheter)	10 (2·8%)
Suprapubic urinary fistula (controlled by catheter)	12 (3·4%)
Epididymitis	3 (0·9%)
Contracture of bladder neck	3 (0·9%)
Chronic urinary infection	14 (4%)

Other complications. Vasectomy was done in 71 patients and 3 of these developed a postoperative epididymitis. In 10 patients it was necessary to introduce a catheter because of severe postoperative haemorrhage. In 12 patients a catheter had to be inserted for some days to control a suprapubic urinary fistula (Table II).

Discussion

In our Department most patients who are admitted with benign prostatic hypertrophy undergo a transurethral resection and an open prostatectomy is performed in only 25-30% of patients. Open (transvesical) prostatectomy is carried out if the adenoma is large and/or there is secondary pathology such as a stone or diverticulum.

The functional results of this procedure compare favourably with those of other techniques. The low incidence of bladder neck stricture is, in our opinion, due to the wide bladder neck and avoidance of the catheter. Some patients develop urinary fistulae after removal of the Redi-Vac drains but this occurred mainly at the beginning of our series when we used a purse string suture to close the bladder. Since then, a two layer running suture has been used and this complication has become rare. If there is severe intraoperative bleeding we would advise against Redi-Vac drainage and would use a transurethral and sometimes a suprapubic catheter for drainage.

The particular advantge of this procedure is the low incidence of urinary infection developing after prostatectomy—11% in this series. The incidence of postoperative urinary infection has been reported to be low especially after transurethral resection, but reports vary from 5 to 52%. In a study of 140 patients, 116 were sterile at the time of prostatectomy but 37 (32%) became infected; there were no differences in the incidence of infection when open and endoscopic prostatectomy were compared (Jackaman and Chisholm, 1975).

In patients with a sterile urinary tract no antibiotics need to be administered postoperatively. In patients with infected urine, a superinfection or change of infection can be avoided. We think that the low incidence of epididymitis is also due to this no-catheter technique. We recommend that preoperative transurethral diagnostic and therapeutic measures are reduced to a minimum in order to avoid infection of the urinary tract. No-catheter prostatectomy seems to be an important aid to maintain asepsis in operative urology.

Summary

A method of no-catheter prostatectomy is described and the results of 350 operations are presented.

It has been demonstrated that this method of prostatectomy can be done aseptically.

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The Authors

G. Hubmer, MD, Professor of Urology.
H. Lipsky, MD, Dozent for Urology.
P. Petritsch, MD, Senior Registrar in Urology.
F. Eppich, MD, Registrar in Urology.

Correspondence to Dr G. Hubmer, Department of Urology, University of Graz, 8036 Graz, Austria.

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Short Case Report

Endometrial Carcinoma of the Prostatic Utricle

A patient, having passed blood per urethram intermittently for 6 years, was diagnosed as having a urethral tumour consistent with carcinoma of the utricle.

Case History

A man aged 58, presenting with haematuria, was found to have a papillary tumour overlying the verumontanum, in the posterior urethra. This was treated on numerous occasions by diathermy, local resection and transurethral prostatectomy. The haematuria not being controlled, a cysto-prostato-urethrectomy was performed and an ileal conduit fashioned.

The operative specimen revealed a tumour lying deep to the prostatic urethra and opening on to its surface in the midline. Arranged in an intricate papillary and glandular manner, the fronds were lined by tall columnar cells with basal nuclei (Fig.). The histological appearances and site were consistent with those of an endometrial carcinoma of the prostatic utricle as described by Melicow and Pachter (1967) and Melicow and Tannenbaum (1971).

Comment

The prostatic utricle is a blind tract running upwards and backwards from the centre of the verumontanum on the dorsal wall of the prostatic urethra. Developing from the Mullerian ducts, it is thought to be homologous with the female uterovaginal canal (Bulmer, 1957). Histologically, a tumour arising from this region resembles an endometrial carcinoma.

The authors are obliged to Mr J. S. Mousley, FRCS for his permission to report this case.

R. Buchanan and J. H. Shepherd
Royal Hampshire County Hospital, Winchester, Hampshire

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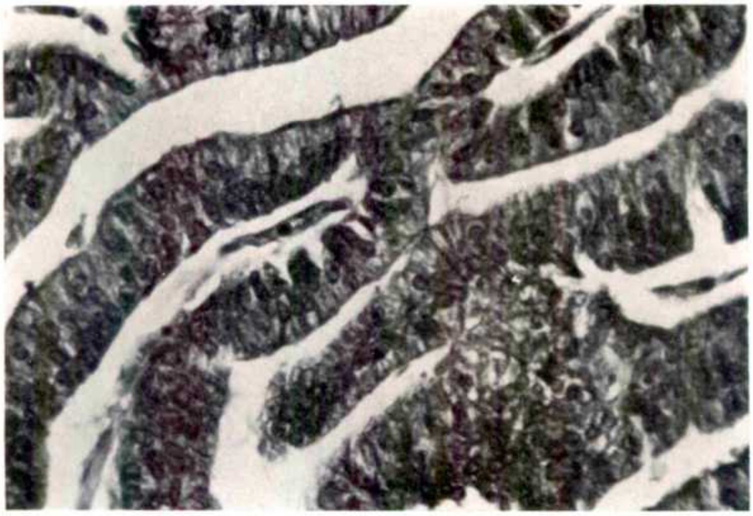

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Cystic Duplication of Ejaculatory Duct: Case Report

G. MOBILIO, A. CAVALLI, M. VALENTE and M. PENNELLI

Department of Urology, Istituti Ospitalieri di Verona and Institute of Pathological Anatomy, University of Padova, Italy

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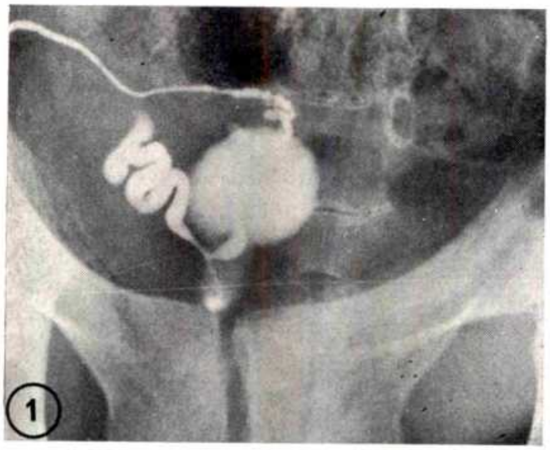
Cystic anomalies of the internal male genitalia are uncommon and often pose a diagnostic problem because they present with indefinite symptoms. Abnormalities of the ejaculatory duct are, without doubt, very rare and, for the most part, congenital, even though an inflammatory pathogenesis has also been proposed for this condition. We describe a case, which presented complex malformation including cystic duplication of right ejaculatory duct.

Case Report

A 26-year-old man admitted in May 1975 to our Department presented with a history of pollakiuria, haemospermia and vague perineal pain. The external genitals were normal, but the head of the left epididymis was increased in size and consistency and was tender. The patient was azoospermic but a previous testicular biopsy had disclosed normal tissue. On rectal examination, a roundish, painless, firm, smooth and rubbery mass was palpated above the prostate and to the right of midline. An IVP, normal on the right, showed no function on the left side; angiographic evaluation confirmed the absence of the left kidney and ureter. A retrograde urethrogram gave negative findings. Cystoscopic examination showed the presence of only the right ureteric orifice, and the right half of the trigone which appeared to protrude. A right vasoseminal vesiculogram outlined a cystic lesion which did not adhere to the seminal vesicle, but covered the ampulla and the proximal portion of the ejeculatory duct (Fig. 1). The left vas deferens could not be identified. Urethroscopy visualised only the right ejaculatory orifice which was catheterised, showing the mass previously described (Fig. 2).

At surgery, the suprapubic extravesical approach was employed since, in this case, it allowed for complete removal of the lesion. Healing was prompt and the patient did not present recurrence of symptoms at follow-up visits.



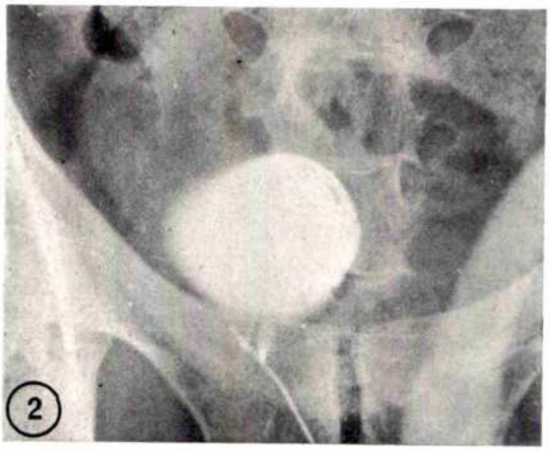
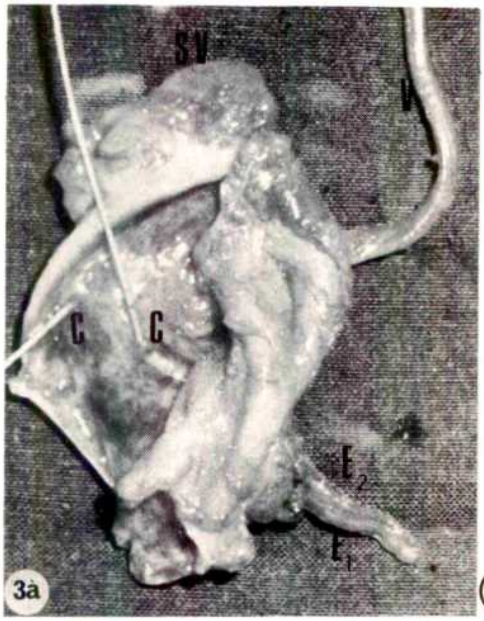


Fig. 1. Vasovesiculogram showing the cyst on the right. Left seminal pathways are not visible.

Fig. 2. Transurethral injection of contrast medium: the two ejaculatory ducts and cyst are clearly visible.



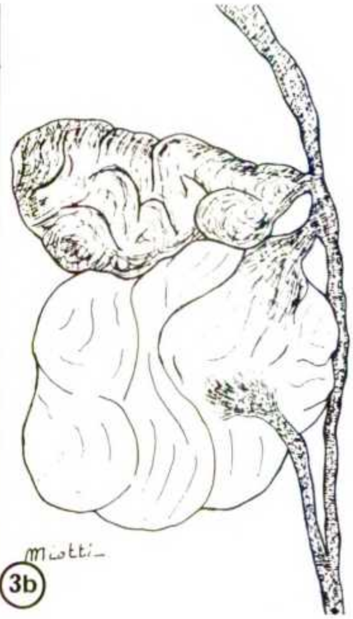


Fig. 3a. The cystic wall has been cut and the cyst opened: the two orifices of ejaculatory duct inside the cavity are indicated by catheters. (C: catheters; V: vas deferens; SV: seminal vescicle; E_1, E_2: ejaculatory ducts).

Fig. 3b. Line drawing of the specimen.

Macroscopically, the specimen consisted of a cystic dilatation of the ejaculatory duct, just below the ampulla of the vas deferens. Another ejaculatory duct arose from the ampulla and coursed along the cyst wall which partially compressed it. The 2 ejaculatory ducts joined together distal to the cyst, before opening into the urethra (Fig. 3). The cyst was 4 cm in diameter and contained a brownish fluid.

Microscopically the cystic wall was formed prevalently of smooth muscular tissue. A columnar type of epithelial lining supported by connective tissue was present, but the inner surface was almost completely ulcerated. Chronic inflammatory cells and collagenous tissue were observed in the wall (Fig. 4). The cystic fluid contained many inactive spermatozoa.

Discussion

Duplication in canalised organs is well documented, but only a few cases regarding the vas deferens have been described (Mysorekar, 1976) and a careful search of the literature disclosed that duplication of the ejaculatory duct has never been reported. Moreover, only 4 cases of cystic formation, or more correctly diverticulum, of the ejaculatory duct were found (Huggins, 1930; Lund and Cummings, 1946; Brooks, 1969; Lucey, Mcaninch and Bunts, 1973) and only one (Brooks, 1969) was described radiologically and histologically.

In our patient, the abnormality involved the seminal pathways of both sides, and the left urinary tract. Abnormal development of the caudal portion of the right Wolffian duct may explain the partial duplication of the ejaculatory duct with cystic dilatation of one branch. On the left, non-development of the mesonephric duct may be responsible for the reno-ureteric agenesis along with the absence of the vas deferens, seminal vesicle and ejaculatory duct.

While our patient did not present clinical signs before reaching adulthood, we consider his anomaly congenital in nature, in view of the various concomitant malformations and the absence of previous inflammatory episodes in the lower urinary tract.

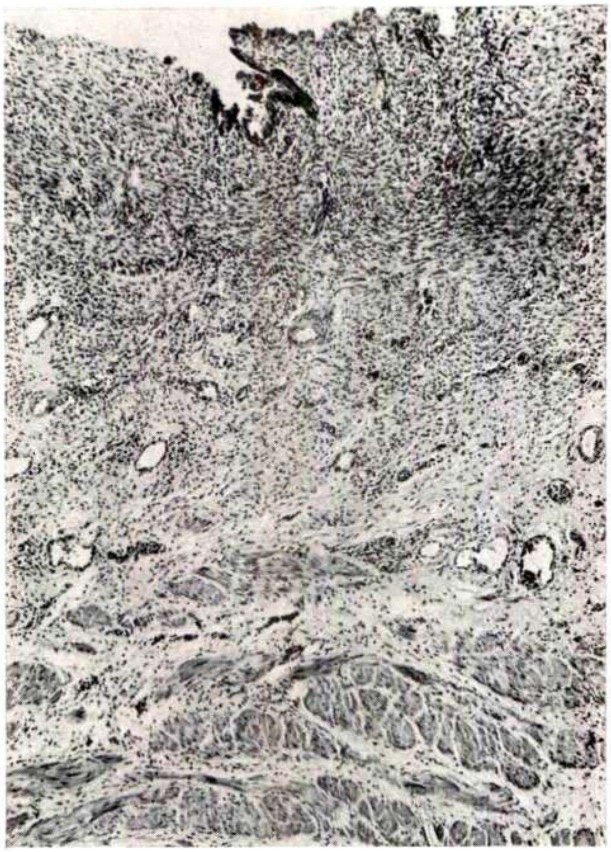


Fig. 4. Histology of the cystic wall showing columnar epithelium lining and muscular layer. H.E. stain, original magnification × 50.

Summary

A case of complex malformation of the genito-urinary tract, including cystic dilatation and partial duplication of the ejaculatory duct is reported.

The lesion was visible on retrograde and anterograde vasovesiculography; its complete removal was possible using an abdominal approach.

We thank Agostino Leorin for the photographs and Patricia Segato for reviewing the manuscript.

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The Authors

Gaetano Mobilio, MD, Professor, Head of Department of Urology.
Achille Cavalli, MD, Assistant Professor, Department of Urology.
Marialuisa Valente, MD, Assistant Professor, Institute of Pathological Anatomy.
Matole Pennelli, MD, Professor, Institute of Pathological Anatomy.

Requests for reprints: Gaetano Mobilio, Department of Urology, Istituti Ospitalieri di Verona.

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Short Case Report

Familial Teratoma of Testis

In a total of 569 testicular teratomas reported to the Testicular Tumour Panel from 1958-67, 2 (0·35%) were in brothers (Pugh, 1976). We should like to report a further such instance.

Case 1

This patient was 20 years old when he presented in 1971 with a 4-month history of swelling and discomfort in the left testis. On examination the testis was enlarged, firm and tender. Its appearance at operation was that of a tumour and orchidectomy was performed. Histology showed it to be a malignant teratoma which would now be classified MTU (Malignant Teratoma Undifferentiated). Lymphograms were not done but radiotherapy was given postoperatively to the para-aortic and pelvic lymphatic areas. He was followed up regularly and remains well with no evidence of metastases 5 years later.

Case 2

This patient was 27 years old when he presented 3 years after his brother with similar complaints of progressive swelling and discomfort in his left testis for the previous 3 months. The testis was found to be enlarged, irregular, firm and tender. The clinical impression was of teratoma and orchidectomy was performed. Histology confirmed this diagnosis and this tumour would also now be classified MTU. His postoperative lymphogram showed invasion of the para-aortic nodes by tumour and shortly after operation the patient developed enlargement of a left supra-clavicular lymph node. Radiotherapy was given to the para-aortic and left supra-clavicular areas, but 3 months later chest X-ray showed multiple pulmonary metastases. Further treatment was given in the form of radiotherapy to the lungs and short courses of cytotoxic agents (vinblastine, actinomycin D and methorexate) every 4 to 6 weeks. However, the patient steadily deteriorated and died 13 months after orchidectomy.

Comment

Although testicular teratoma is uncommon, its incidence has risen from 0·4 per 100,000 males in 1958 to 1·26 per 100,000 males in 1971 (Pugh, 1976). Despite improved radiotherapy and chemotherapy the tumour has a mortality rate of about 10% when lymphograms do not demonstrate retroperitoneal metastases at the time of orchidectomy and about 50% when such involvement is seen (Peckham and McElwain, 1974). Although familial testicular teratoma is rare, male relatives of patients should be warned to consult their doctor as soon as possible if they develop testicular enlargement or discomfort. We consider that the delay of 3 months by our 2nd patient between the onset of his symptoms and his seeking medical advice may have contributed significantly to his death.

W. O. Thomson and D. M. Sinclair
Division of Surgery, Royal Infirmary, Glasgow

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Parameatal Urethral Cysts: a Review of 6 Cases

J. T. HILL and M. HANDLEY ASHKEN

Urological Department, Norfolk and Norwich Hospital, Norwich

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Cyst formation in the parameatal area of the urethra was first reported in 2 male cases as recently as 1956 by Thompson and Lantin. Further reports have been rare, but 6 similar cases have been documented in the Norfolk area during the past 4 years. They are described below.

Case Reports

Case 1. R. G., a male aged 21 years, presented with a cystic swelling of the urethral meatus for 2 years, following a gonococcal urethritis. This had ruptured and recurred on several occasions but had caused no urinary or sexual problems. A cyst, 1 cm in diameter was noted, at the external meatus. This was excised under general anaesthesia; postoperative progress was uneventful. Histological examination showed the lining to be of columnar epithelium with areas of chronic inflammation and mucoid degeneration. A 12-month follow-up has revealed no recurrence.

Case 2. J. G., a male aged 8 years, presented with a cystic swelling of the urethral meatus for 6 weeks. There were no urinary symptoms. Physical examination confirmed a small urethral cyst at the meatus, tethered to the frenulum. This was excised under general anaesthesia. Postoperative progress was uneventful. Histological examination showed chronic inflammatory foci with a columnar epithelial lining. A 12-month follow up has revealed no recurrence.

Case 3. K. H., a male aged 22 years, presented with a cystic swelling at the penile meatus for 2 years (Fig. 1). This caused no symptoms. Examination confirmed a small parameatal cyst, 1 cm in diameter, associated with a monilial balanitis. The cyst was excised under general anaesthesia. Postoperative recovery was uneventful. Histological examination showed a tall columnar epithelial lining with no evidence of inflammation. A 3-month follow-up has revealed no recurrence.

Case 4. C. D., a female aged 21 years, presented with a vulval swelling for 5 months. This caused discomfort on micturition and had slowly increased in size. Examination showed a cyst, 1·5 cm in diameter, to the left of the urethral meatus. An intravenous pyelogram showed no abnormality. The cyst was excised under general anaesthesia. Postoperative progress was uneventful. Histological examination showed a lining of partly squamous epithelium and partly chronic granulation tissue. A 7-month follow-up has revealed no recurrence.

Case 5. G. M., a female aged 27 years, presented with a vulval swelling for 4 months. There were no urinary or sexual problems. Examination showed a cyst of the urethra 1·5 cm in diameter lying to the left of the meatus (Fig. 2). Intravenous pyelography showed no abnormality. The cyst was excised under general anaesthesia. Postoperative recovery was uneventful. Histological examination showed a lining of transitional epithelium, with no inflammatory tissue. A 6-month follow-up has revealed no recurrence.

Case 6. K. H., a female aged 25 years, was found to have a parameatal urethral cyst on routine vaginal examination during pregnancy. She had been unaware of the cyst, and was asymptomatic. After completion of the pregnancy, the cyst was excised under general anaesthesia. It contained thick yellowish fluid. Histological examination showed a transitional cell epithelial lining with no evidence of inflammation. Postoperative progress was uneventful; the cyst did not recur during a 4-year follow-up.

Discussion

Very few cases of parameatal cysts have been recorded in the world literature. Thompson and Lantin reported 2 male cases in 1956, Rocchi, Levati and Guidice reported 3 cases in 1968, and Shiraki reported 9 cases in 1975. No reports have so far been recorded in the British literature. The relatively high incidence of cases in Norfolk is not easily attributed to any local factors, but might suggest the condition is in general more common than is apparent on reading the literature.

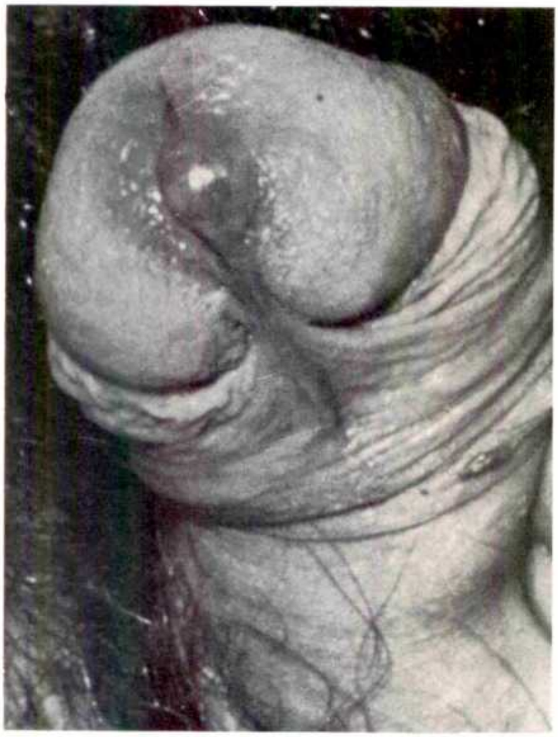


Fig. 1. A male parameatal cyst (case 3).

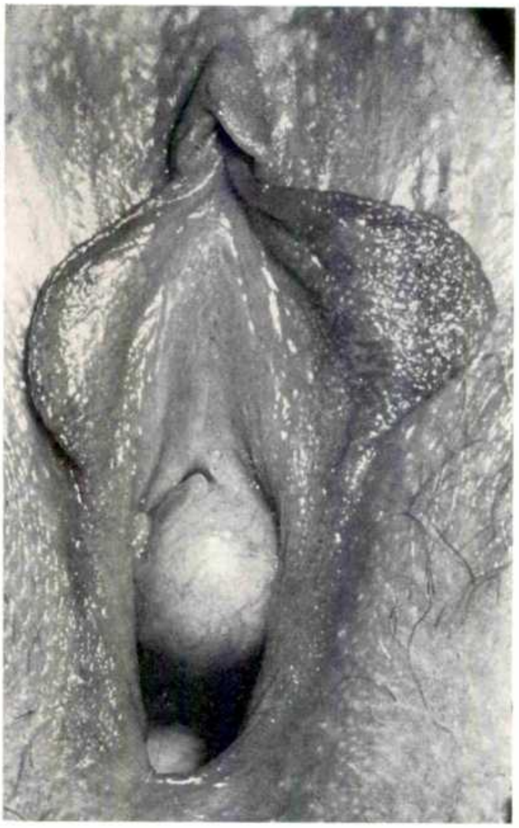
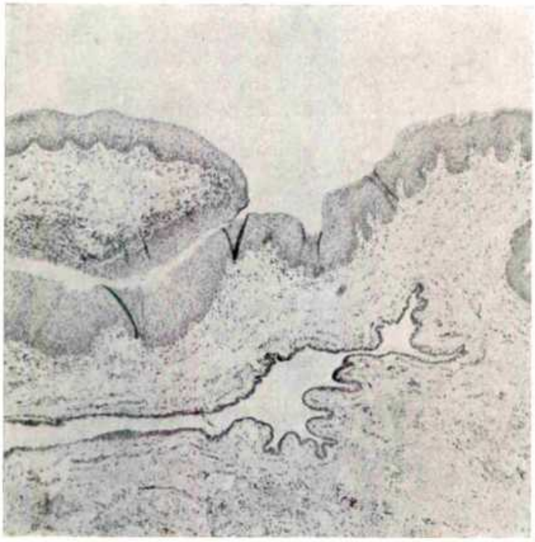


Fig. 2. A female parameatal cyst (case 5).



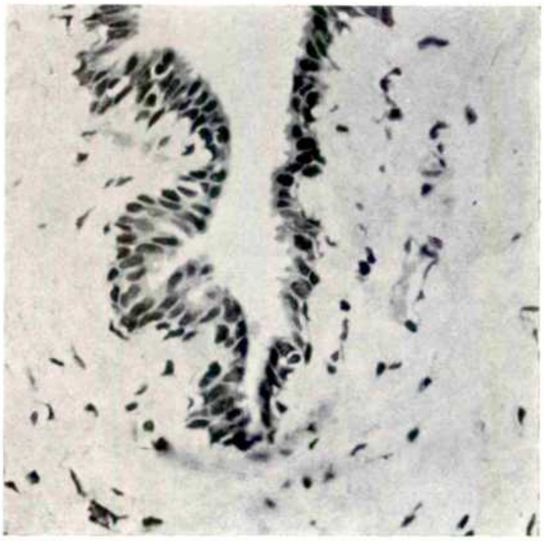


Fig. 3. Histological appearance of a parameatal cyst lining from case 2. × 120.

Fig. 4. Histological appearance of a parameatal cyst lining from case 2. × 480.

The aetiology of these cysts is not completely understood. The urethra is formed during ventral fusion of the urethral folds which results in the ventral median raphe. Thus any resulting cyst formation would occur on the ventral aspect of the penis in the midline. However, the cysts described above occur at the lateral margin of the meatus (Figs. 1 and 2). Thompson and Lantin (1956) suggested they formed during the process of preputial separation from the glans penis. They demonstrated such cystic areas in sagittal sections of a normally developing 7½ and 8-month embryonic glans penis. However, they also stated that faulty preputial separation usually resulted in cyst formation along the coronal sulcus of the glans penis. If the aetiology was congenital one would expect the cysts to appear in childhood. In this series, only 1 case was a child, the others were all young adults. It has been suggested by Shiraki (1975) that the cysts are caused by blockage of the para-urethral ducts rather than the glands of Littré because the latter do not extend distally beyond the fossa navicularis. This explanation seems more acceptable in our cases. Trauma and circumcision are unlikely causes of parameatal cyst formation because none of our male cases had been circumcised and only 1 out of 6 cases admitted to a history of trauma. Infection could be an aetiological factor as evidence of chronic inflammation was found in the cysts of cases 1, 2 and 4. Case 3 was also found to have a severe monilial balanitis.

The cysts are usually small, averaging about 1 cm in diameter. They occur on the lateral margin of the urethral meatus and may be bilateral (Thompson and Lantin, 1956). None of our cases suffered more than one cyst simultaneously. They may be diagnosed as a coincidental finding and be asymptomatic, or they may cause pain during micturition and sexual intercourse. When the cyst is traumatised it may bleed, rupture or become infected. The length of history ranges from 16 weeks to 2 years.

The cyst wall epithelium may be columnar, squamous or transitional (Figs. 3 and 4). In 5 cases the cyst content was a clear fluid, the 6th case contained a thick yellowish fluid. The differential diagnosis rests between inflammatory conditions of the urethral meatus, prolapsing ureteroceles (especially in females) and duplications. A full urological investigation, including urography and cysto-urethroscopy is therefore advisable.

The treatment of choice is complete excision. Simple decapping results in a recurrence (Shiraki, 1975). Total excision of the cyst leaves very little deformity, although Rocchi *et al.*, reported one case of postoperative urethral stenosis. In male cases circumcision was not considered necessary for the prevention of cyst recurrence.

Summary

6 cases of parameatal urethral cysts are reported in 3 males and 3 females.

The condition is considered to be rare.

The aetiology is thought to be obstruction of the para-urethral ducts possibly due to infection.

The treatment of choice is complete excision.

We wish to thank Mr C. G. Gaches for allowing us to report his cases and for help in writing the article. We wish to thank the department of photography, Norfolk and Norwich Hospital and Miss J. Nicholls for secretarial assistance.

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The Authors

J. T. Hill, FRCS, Registrar in Urology.
M. Handley Ashken, MS, FRCS, Consultant Urologist.

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Short Case Report

Malignant Priapism

Priapism is characterised by persistent painful erection unrelated to sexual excitement, and it is called malignant whenever the priapism is due to metastases. Metastases to the penis from renal cell carcinoma producing priapism are very rare. The following is a report of such a case.

Case Report

T. C., a 75-year-old male, was admitted to the Hospital, complaining of persistent priapism of 6 months' duration. On close examination the patient admitted having had haematuria on and off for a similar duration. The patient looked cachectic; the left kidney was palpable, non-tender; scrotum and testis were normal; the penis was erect and tender to touch. An intravenous pyelogram showed a non-functioning left kidney with spotty calcification. Chest X-ray and X-ray of spine were normal. Blood count was essentially normal. Cystoscopy was unremarkable.

A clinical diagnosis of left renal cell carcinoma was made and radical nephrectomy was performed. During operation invasion of the left renal vein by the tumour was noted. Subsequent histology reported this to be a renal cell carcinoma of an anaplastic type. No cause for priapism was found. The patient was discharged from hospital. He was re-admitted 8 weeks later complaining of acute urinary retention, priapism and pain in the penis. Because of the difficulty in micturition and the pain, the patient underwent complete amputation of the penis and perineal urethrostomy—after other methods of treatment for the priapism had failed. Histological examination of the penis showed extensive metastatic deposition of renal cell carcinoma (Figs. 1 and 2). The patient died on the 10th postoperative day due to pulmonary embolism.

Comment

Secondary deposits from renal cell carcinoma in the penis are extremely rare. Only 160 cases with penile metastases due to various neoplasms have been reported but of these only 13 cases were due to renal neoplasms.

Priapism is not a feature of metastatic lesions of the penis but it was a feature of all the reported cases of metastasis in the penis due to hyper-nephroma (Smith and Benacorti, 1964).

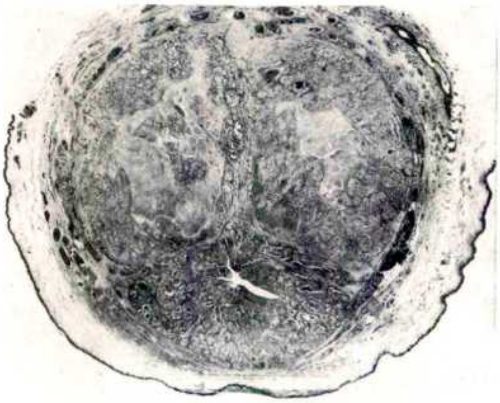

Fig. 1.

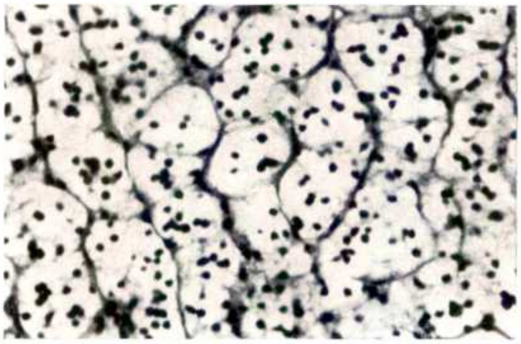

Fig. 2.

Radical approach would hardly seem indicated, as priapism has been a terminal feature of this disease. However, radical amputation has been successful in other forms of metastatic penile lesions. We failed to diagnose the condition before the amputation of the penis.

A. Sriman Narayana, D. G. Kelly and F. A. Duff
Department of Urology, St Vincent's Hospital, Dublin

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Ultrasonic Evaluation of Scrotal Swellings

KENJIRO KOHRI, SUSUMU MIYOSHI and ATSUSHI NAGAHARA
Department of Urology, Higashiosaka Central Hospital, Osaka, Japan

(Received 19 July 1976; accepted for publication 18 January 1977)

Diagnostic ultrasound has the ability to delineate soft tissues and, unlike X-rays, has not been shown to have harmful biological effects on tissues at diagnostic levels. It is non-invasive, quick and painless. It is, therefore, an ideal method of evaluating scrotal swellings. In the clinical examination of a scrotal mass, transillumination is frequently employed to detect fluid-filled structures such as hydroceles. Sonography is a sophisticated advance on transillumination. It has a unique diagnostic potential in urology since it can differentiate fluid from solid tissue and can give two-dimensional representation of organs and masses.

Patients

Examinations were carried out on 18 patients with scrotal swelling, 6 with unilateral hydrocele, 1 with bilateral hydroceles, 3 with testicular neoplasm, 3 with inflammation, 2 with torsion of a testicle, and single examples of scrotal trauma, hernia with air-filled intestine, and inguinal cryptorchidism with hydrocele and varicocele.

Method

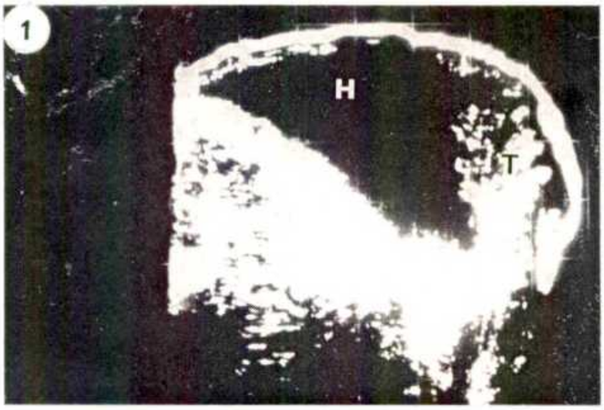
Our examinations were performed with Hewlett-Packard Inc. ultrasonic apparatus with a 2·25 MH_z transducer. Images were stored in a persistence oscilloscope and Polaroid photographs obtained for permanent record. The patient was placed supine and the legs were spread apart. Originally we supported the scrotum with the left hand and scanned with the transducer held in the right hand. The hand, however, caused confusing posterior echoes making it difficult to evaluate the entire structure.

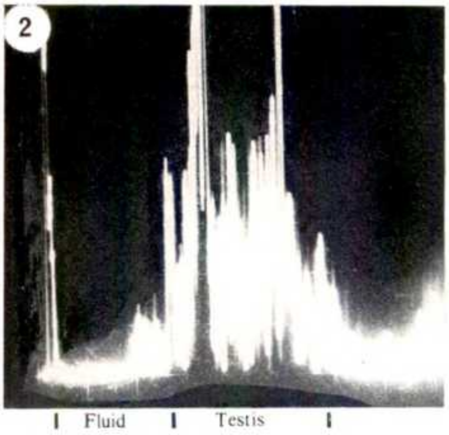
We, therefore, now use a sponge under the scrotum. After application of mineral oil to the scrotum, the scrotum is scanned longitudinally with both lower and high gain settings. The sponge support allows transverse scanning as well, although longitudinal scanning appears to be more useful. The limit of resolution was 1 mm. Simultaneous A- and B-mode scans were used. The sliding of the transducer on the scrotal skin sometimes caused reflex movements in younger men. In such cases, A-mode, which does not involve sliding of the transducer, is better than B-mode.

Case Reports

Case 1

A 53-year-old man, presented with a 6-year history of unchanged bilateral scrotal swellings. Physical examination showed bilateral soft, infant's head sized scrotal masses, both of which were too large to transilluminate. The penis was buried in the scrotal swellings. The testes could not be identified. On B-scan, large fluid-filled areas were seen anterior to the testicles. In addition, solid plaque-like structures were present lying along the posterior wall. These were suspected to represent local inflammation. Exploratory surgery revealed hydroceles containing about 500 ml and 350 ml of straw-coloured fluid in the right and left scrotum respectively. The posterior wall plaques were fibrous granulation tissue secondary to chronic epididymitis (Fig. 1).





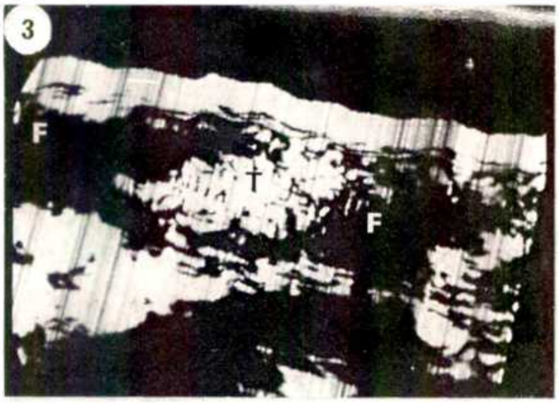


Fig. 1. Case 1. Longitudinal B-scan shows the clear echo-free large hydrocele (H) lying anterior to a testicle (T).

Fig. 2. Case 2. A-scan demonstrates that there are no internal echoes. On B-scan, the pattern was almost similar to case 1.

Fig. 3. Case 3. The testis (T) is surrounded by fluid (F). At surgery the cryptorchidism with hydrocele and varicocele was found.

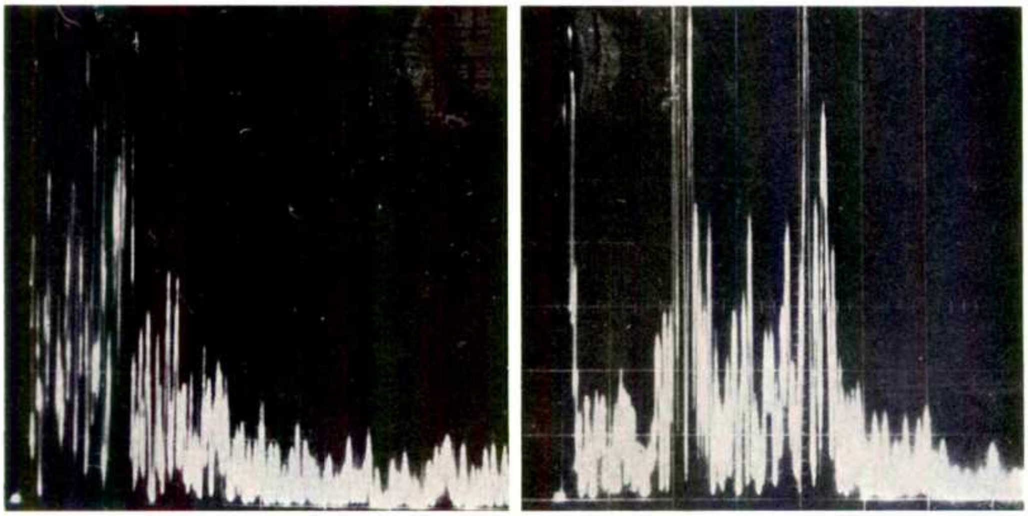


Fig. 4. (a), Normal A-scan of the testicle.
(b), Testicular neoplasm. There are internal echoes.

Case 2

A 58-year-old man, who had a past history of aplastic anaemia, presented with a 2-month history of a right scrotal swelling. The firm mass measured 10 × 7 × 5 cm, was non-tender and transilluminated. On B-scan, a fluid-filled structure was seen occupying the anterior portion of the scrotal sac, and the testis was normal in size (Fig. 2). Since he had a history of aplastic anaemia, exploratory surgery could not be done and the scrotal swelling has been serially examined on B-scan. Straw-coloured fluid aspirated was cytologically negative. Polaroid photographs of the scans provide permanent records and were useful for the purpose of follow-up comparison.

Case 3

A 4-year-old boy, was found to have an empty scrotum on the left side. A tumour palpated in the left groin was larger than a normal testis and his right testis. Malignant change in an undescended testis was suspected. Transillumination could not be assessed because of its site. On B-scan, the testis of 2 cm in diameter was surrounded by fluid (Fig. 3). At surgery an undescended left testis with a hydrocele and varicocele was found and orchidopexy was performed.

Case 4

A 20-year-old man, presented with a 1-month history of a right scrotal swelling. On physical examination, a painless, firm, non-transilluminating, hard mass measuring 5 × 3 × 4 cm was found. Laboratory findings showed d-fetoprotein and urine HCG to be positive. He was apyrexial. A-scan showed that there were internal echoes, and a high gain setting was needed for penetration (Figs. 4a and 4b). Testicular neoplasm was suspected and orchidectomy was performed. Histology demonstrated embryonal testicular carcinoma.

Case 5

A 13-year-old boy who had been kicked in the scrotum 3 days previously presented with a scrotal swelling. The mass measured 5 × 4 × 3 cm, was painful, hard and non-transilluminating. B-scan showed that there was swelling of the scrotal content but no haematoma. 2 months after the accident, the swelling disappeared.

Case 6

A 37-year-old man, presented with a 2-hour history of right scrotal swelling and violent pain after heavy lifting. Prehn's sign was positive. He had slight fever. The B-scan could not differentiate torsion from inflammation. We presumed torsion of the testicle and this was confirmed at operation.

Discussion

Our study was of 18 patients, who had sonography and anatomical diagnosis of scrotal swellings. With the exception of 2 cases of torsion, 16 cases were correctly diagnosed. The 12 cases not described in detail give similar scan findings in the same diseases. All of the hydroceles showed a clear echo-free interior. Boyce and Politano (1970) mentioned that the outstanding characteristic of hydrocele is translucency, except in the cases in which the parietal tunica has become so thickened that it no longer transmits light, and that the differentiation of hydrocele from hernia may be difficult if the hernia cannot be reduced. In addition, haematoceles, chyloceles, and pyoceles do not transilluminate. The fluid-filled nature of all of these swellings is more recognisable on B-scan. In these cases, it is useful to use ultrasound, since it can differentiate fluid from solid tissues. The testis is situated in the posterior and lower portion of a hydrocele swelling and a spermatocele is usually a distinct mass situated above and behind the testis. The B-scan examination will distinguish these diseases since it can show the anatomical situation. On B-scan, Miskin and Baum (1974) found that the normal testicle is primarily sonolucent but that internal echoes are found if the testis is rotated, bringing the rete testis into the plane of the scan. Of more importance was the finding of an asymmetrical cluster of internal echoes in their 2 cases of testicular neoplasm.

In Case 1, the solid plaque-like structure, ultrasonically visualised and found to be in the posterior scrotum, proved to be chronic epididymitis.

As ultrasonic diagnosis is non-invasive, safe and pain-free; repeated examinations can be performed.

Although we examined only 1 case, B-scan examination is valuable in distinguishing a hydrocele from a hernia. Differentiation of a hydrocele from a hernia on clinical examination may occasionally be difficult especially if the hernia cannot be reduced. Infants present a particular problem as there are no sure clinical signs to distinguish between congenital hydroceles and congenital hernias. Since diagnosis by aspiration is contra-indicated in children, ultrasound should be valuable in detecting simple hydroceles. These can frequently be managed conservatively. A hernia is present if air is found within the scrotum. This is easily shown by B-scan when there is non-penetration by the sound beam.

In Case 3, B-scan examination showed the left inguinal cryptorchism to be surrounded by fluid, which at operation was found to be a hydrocele and varicocele.

Torsion of the testicle, however, could not be diagnosed definitely on A- or B-scan. In our 2 cases, the presenting history and physical examination ruled out an infection. Pedersen *et al.* (1975) state that Doppler ultrasound is valuable in diagnosis of testicular torsion. The presence or absence of intratesticular arterial pulsation could be demonstrated, and a correct diagnosis was made in 5 patients with testicular torsion and 10 patients with epididymitis.

Summary

Scrotal swellings in 18 patients were examined by ultrasound.

Sonography can differentiate fluid from solid masses.

All but 2 patients who had torsion of the testicle were correctly diagnosed prior to operation. Although this is only a preliminary report, it does demonstrate that useful information may be obtained by this method.

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The Authors

K. Kohri, MD, Attending Staff (now Associate, Department of Urology, Kinki University School of Medicine).
S. Miyoshi, MD, Attending Staff.
A. Nagahara, MD, Chief.

Requests for reprints to Dr K. Kohri, Department of Urology, Kinki University School of Medicine, Sayama-cho, Minami-Kawachi-Gun, Osaka, Japan 589.

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A Papilloma of Epididymis of Müllerian Vestigial Origin

J. S. CURRIE and G. NGAEI

Departments of Pathology and Surgery, Western Infirmary, Glasgow

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The purpose of this article is to describe a benign tumour of the epididymis, apparently arising from the Müllerian vestiges in close proximity to the epididymis. We have been unable to find a description of a similar case in the literature.

Case History

A 48-year-old man presented with a painful right-sided scrotal swelling of 30 hours' duration. He gave a history of similar episodes occurring over the past 20 years. On these previous occasions a right scrotal swelling developed which would last for a few hours and resolve spontaneously; however on this occasion the swelling persisted and became painful. The patient gave no history of scrotal trauma.

On examination a right hydrocele was diagnosed and 200 ml of slightly blood-stained straw-coloured fluid was aspirated. Following aspiration a 20 mm firm mobile lump related to the lower pole of the right testis became palpable.

Cytological examination and culture of the aspirate were negative.

The patient was discharged and when seen again 2 weeks later the hydrocele had recurred and excision was therefore advised. After excising the hydrocele sac, a polypoid nodule was seen arising from the epididymis adjacent to the lower pole of a normal testis: it was also excised.

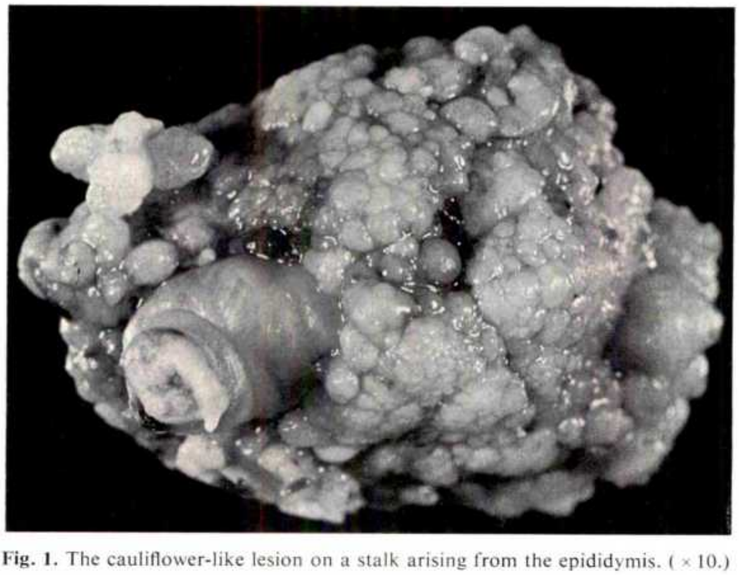

Fig. 1. The cauliflower-like lesion on a stalk arising from the epididymis. (× 10.)

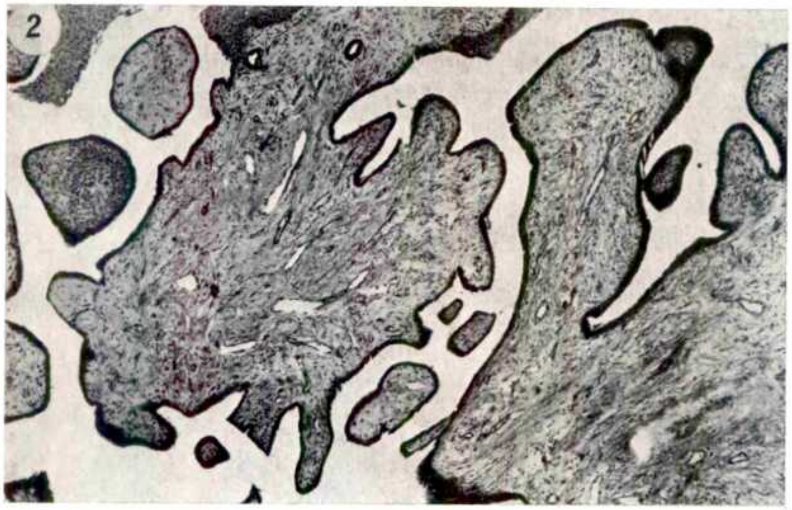

Fig. 2. The frondose structure of the lesion with squamous epithelium in places. (H & E. × 38.)

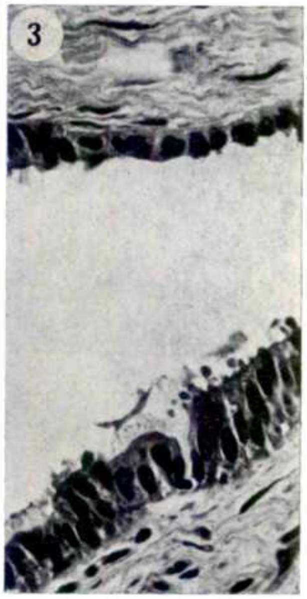

Fig. 3. Low cuboidal and ciliated columnar epithelium with the "hob nail" appearance of the latter. (H & E. × 370.)

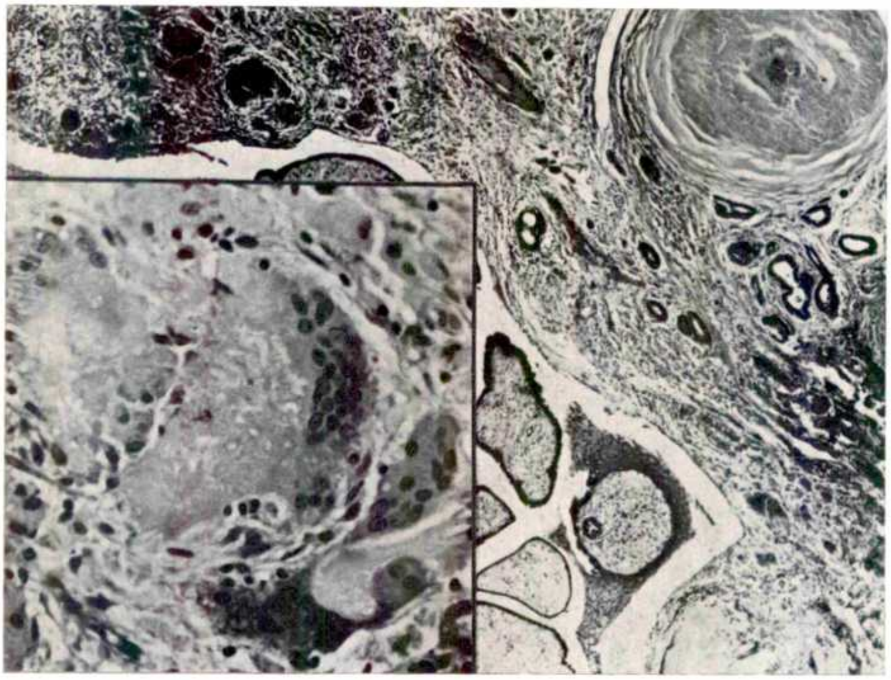

Fig. 4. The ductular elements with inspissated secretions and an associated giant cell reaction. (H & E. × 38.)

Pathology

The specimen was a firm pedunculated warty nodule (20 mm diameter) with a cauliflower-like surface on a 10 × 2 mm stalk (Fig. 1). On cross-section, radiating connective tissue septa, taking origin from the stalk and giving the lesion a papillomatous appearance, were seen.

Histological examination showed a papillomatous lesion with a collagenous fibrous tissue core. In areas the collagen was hyalinised and focally calcified and there were many dilated vascular and lymphatic channels. The surface was markedly irregular and bore numerous epithelium-covered papillary fronds (Fig. 2); the epithelial lining varied from a low single layer of cuboidal epithelium to a ciliated columnar epithelium which showed a focal "hob nail" appearance of its component cells (Fig. 3), to a stratified squamous epithelium with patchy surface keratinisation. There were areas of ulceration, evidence of old haemorrhage and chronic inflammatory foci with foreign body type giant cells and lymphocytes. Within the stroma there were duct-like structures lined by flattened cuboidal epithelium and some of these contained inspissated secretions forming whorled acellular deposits (Fig. 4).

Discussion

A review of the literature has failed to reveal a description of a similar lesion.

There are two possible diagnoses. First, a "reactive" nodule which has developed as a consequence of repeated irritation of the tunica vaginalis by recurrent hydroceles. Secondly, a rare neoplasm which has been the cause of the recurrent hydroceles.

The history of repeated hydrocele supports a reactive origin, and Dr R. C. B. Pugh (personal communication) believed this was a possible explanation. However, the unusual histology of the nodule, the lack of inflammatory cells in it, the marked keratinisation and the absence of metaplasia from the tunica (except in the nodule) are strongly suggestive that the basic lesion is neoplastic and the hydrocele is a consequence of it (perhaps due to the liberation of keratin into the sac.)

We think that this is a benign tumour arising from the Müllerian vestiges which are to be found at varying levels adjacent to the epididymis (Sundarasivarao, 1953; Willis, 1967). Proliferation and cystic dilatation of the Müllerian epithelium have been described (Sundarasivarao, 1953).

The epididymal tumour which most closely resembles the case here reported is the adenomatoid tumour as described by Jackson (1958) but the differences between them are quite marked. In our case the tumour does not contain muscle fibres, it is much more papillary and the degree of squamous metaplasia is much greater than that usually to be found in an adenomatoid tumour. The lesion which most closely resembles the one under discussion was described by Selzer and Nelson (1962) as a benign papilloma of the cervix uteri in children.

We believe that the tumour under discussion is an unusually well-differentiated papilloma of the family of Müllerian vestigial tumours (Willis, 1967) and this view is shared by Professor R. A. Willis (personal communication).

Summary

A 20 mm diam. nodule attached to the lower pole of the epididymis was found in a 48-year-old man presenting with recurrent hydrocele.

Histology showed a benign papillary tumour of a type apparently not previously described. It is believed to have arisen from Müllerian remnants.

The authors would like to acknowledge the opinions given to them by Professor R. A. Willis and Dr R. C. B. Pugh, and the assistance in preparing this article from Professor B. Lennox.

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The Authors

J. S. Currie, MB, ChB, Senior House Officer, Department of Pathology (now Senior House Officer, Department of Clinical Surgery, University of Edinburgh).

G. Ngaei, FRACS, Registrar, Department of Surgery.

Requests for reprints to Dr Currie, Department of Clinical Surgery, University of Edinburgh, Edinburgh.

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The Significance of Retroperitoneal Lymph Node Morphology in Testicular Tumours

M. A. S. JEWETT, S. I. HADJU, R. A. GOOD and W. F. WHITMORE, JR
Memorial Sloan-Kettering Cancer Center, New York, USA

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The role of the regional lymph nodes and afferent lymphatics in cancer has been extensively studied and it has been suggested that they are important in the initiation of an anti-tumour immune response (Karpas and Madden, 1973; Perez, Stewart and Wagner, 1975). This conclusion is largely based on animal work as studies in humans are limited by the obvious difficulties of obtaining material from patients with evolving malignancy. Most observations have been made after the disease is clinically apparent and therefore well established. Non-neoplastic changes in lymph node morphology have been described (Cottier, Turk and Sobin, 1972) and it has been suggested that histological evidence of lymphoid activity reflects a host response to the tumour which can be correlated with prognosis (Tsakraklides, Tsakraklides and Good, 1974).

In this study, the retroperitoneal lymphadenectomy specimens from patients with testicular cancer were reviewed retrospectively and the lymph node morphology, primary tumour histology, and prognosis were compared.

Materials and Methods

A total of 42 cases were reviewed which met the criteria of a primary germinal tumour of the testis treated by retroperitoneal lymphadenectomy before any other form of therapy. Only those cases with complete pathological material for study and with a minimum of 2 years' follow-up were included (although most have longer follow-up). 2 years is a sufficient period because more than 85% of the ultimate deaths occur within 2 years (Whitmore, 1968).

By primary tumour histology, there were 36 non-seminomas (embryonal carcinomas with or without teratoma and choriocarcinoma elements) and 6 classical seminomas. The seminomas represented all the available material that met our criteria. 16 patients had had preoperative pedal lymphangiography. The lymphadenectomy specimens had been geographically subdivided at the time of surgery (Ray, Hajdu and Whitmore, 1974) and the nodes from each area were reviewed. According to the degree and pattern of lymphoid activity, each node was classified as stimulated or unstimulated. If a mixed picture was seen, the predominant pattern was selected. Initially, the method of Tsakraklides, Tsakraklides, and Good (1974) was attempted (Fig. 1) in which a node is designated either: (1) "lymphocyte predominant" in the presence of expansion of the deep cortex; (2) "germinal centre predominant"; (3) "lymphocyte depleted"; or (4) "unstimulated". However, because of the frequent mixture of the 2 patterns of stimulation, both within single nodes and among the same group of nodes, the designation of stimulated was used for both (i) and (ii).

Results

The initial 16 cases reviewed had had diagnostic lymphangiography prior to surgery. This procedure was found so to alter nodal architecture with initial pooling of the dye and subsequent disruption and fibrosis, that interpretation was not possible. The remaining non-seminoma cases were therefore selected consecutively from the period 28 January, 1971 to 21 October, 1971 (only those that met all criteria) which was before the use of routine preoperative lymphangiography.

Of 20 patients with non-seminomas (Table I), 15 had a stimulated pattern. 4 of the 15 died of disease by 2 years giving a crude survival rate of 73·3%. Of the 5 unstimulated, 1 died for a survival rate of 80%. The remainder were alive and free of disease for 2 or more years. There was no correlation between pathological stage, nodal pattern and prognosis (Table II). Because of the

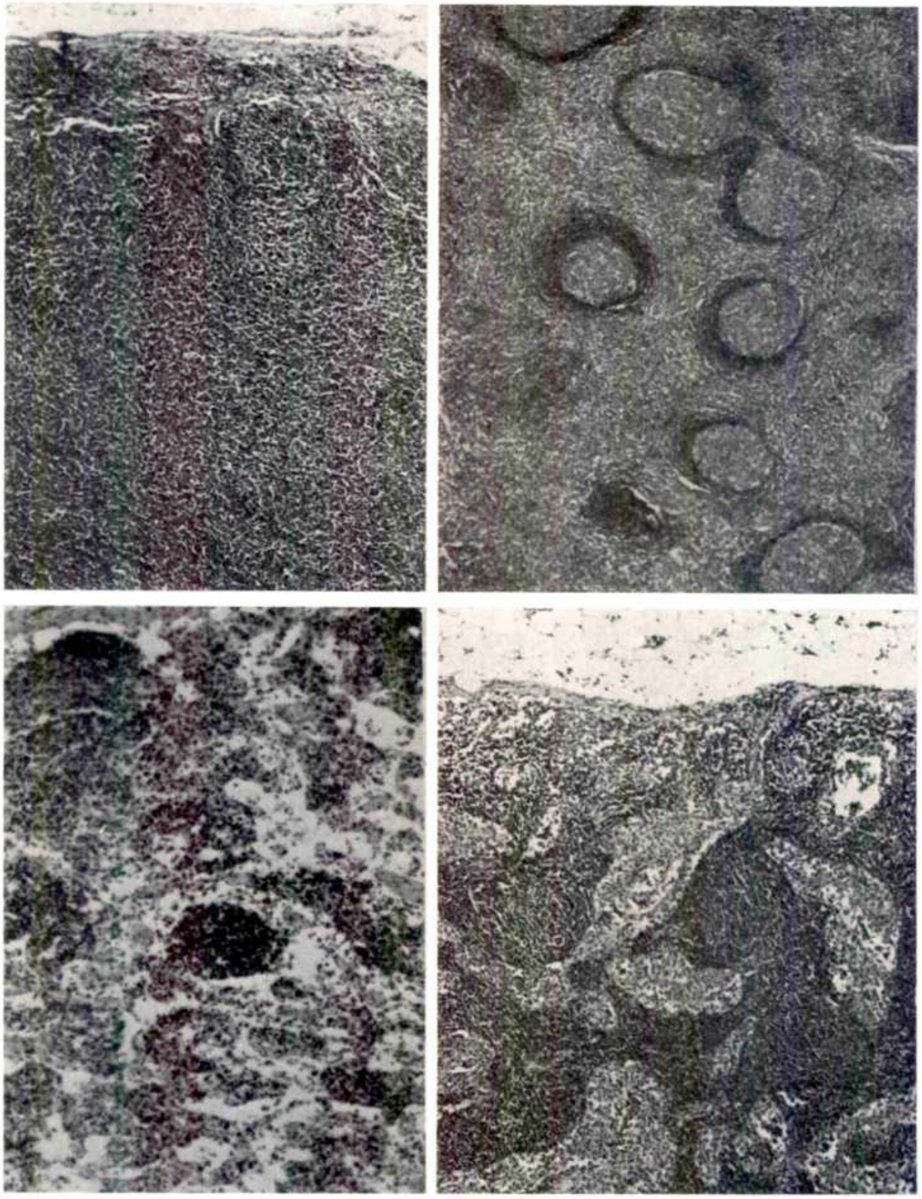

Fig. 1. Photomicrographs of the 4 patterns of lymph node morphology described by Tsakraklides *et al.* (1974). (A) "Lymphocyte predominant" with expansion of the deep cortex. (B) "Germinal centre predominant". (C) "Lymphocyte depleted". (D) "Unstimulated"

lack of correlation and low degree of stimulation after the review of 20 cases with non-seminomas, the study was not extended. Compared to the nodal patterns seen with other tumours, unstimulated nodes frequently verged on lymphocyte depletion and stimulation patterns were much less marked and rarely uniform throughout a node.

Of the 6 patients with classical seminoma, 2 had nodal hyperplasia that was both "germinal centre" and "lymphocyte predominant". This was more pronounced than in any of the non-seminoma cases, however, in the remaining 4 cases, the predominant pattern was unstimulated.

Discussion

Although the clinical course of a patient with cancer is largely determined by the tumour's malignant potential, host factors including the immune response, are also important. The regional lymph nodes comprise one level of the immune system that may be studied to assess the presence and degree of such a response. The morphology of the nodes has been suggested as one measure of function and Black and Speer (1960) first correlated reactivity with improved survival in patients with breast cancer. This work has been extended and the pattern of lymphoid reactivity emphasised by Tsakraklides *et al.* (1974). The germinal centres appear to be chiefly comprised of non-T-cells, subpopulations of which are known to produce antibody and therefore mediate the humoral immune response (Cottier *et al.*, 1967). The paracortical region or deep cortex contains T-cells which are responsible for the cell-mediated immune response (Parrott, deSousa and East, 1966). On this basis, the type as well as the degree of response may be evaluated.

However, not all tumours seem to produce the same degree of response in their draining nodes. According to reports, cancers of the head and neck (Berlinger *et al.*, 1976), breast, cervix (Tsakraklides *et al.*, 1974), and bladder (Herr, Bean and Whitmore, 1976), have a better prognosis if the nodes show evidence of stimulation and a much worse prognosis with nodes that are depleted of lymphocytes. These findings could not be reproduced for colorectal cancer

Table I

Prognosis According to Lymph Node Morphology

Tumour type	No. of patients	Lymph node morphology	No. of patients	2-yr-survival*
Seminoma	6	Stimulated	2	100% (2/2)
		Unstimulated	4	100% (4/4)
Non-seminoma	20	Stimulated	15	73% (11/15)
		Unstimulated	5	80% (4/5)

* None lost to follow-up, all survivors disease free, most followed longer and remained disease free.

Table II

Prognosis according to Stage and Lymph Node Morphology

Tumour type	No. of patients	Pathological stage	Survived stimulated	Survived unstimulated
Seminoma	5	A	100% (2/2)	100% (3/3)
	1	B	–	100% (1/1)
Non-seminoma	11	A	79% (7/9)	100% (2/2)
	9	B	67% (4/6)	67% (2/3)

(Tsakraklides *et al.*, 1975) or soft tissue sarcomas (Hajdu, Shiu and Fatner, in press) and, now with this report, by reviewing a small number of testicular tumours.

With testicular tumours, these differences may be due to the problem of determining which of the retroperitoneal nodes represent the primary draining area. Ray *et al.* (1974) described the pattern of metastases and the complexity of the testis lymphatic drainage but it is not always easy to determine which node in a surgical specimen is the primary one. As well, if the predominant pattern in one area is different from another, it sometimes is difficult to decide which overall designation should be used. Clearly the contralateral iliac nodes are less significant than the inter-aortocaval, for example. This produces a sampling error that could obscure evidence of an immune response.

A second explanation may be a variation in the degree of antigenicity of different tumours or the hosts' ability to respond to the antigenicity. There is little information on the role of the immune system in patients with testis tumours. *In vivo* skin testing with dinitrochlorobenzene (DNCB) and common antigens has been used as a measure of cell-mediated immune responsiveness. Preliminary data showed that non-seminoma testicular patients with metastatic disease had a slightly decreased rate of response to DNCB but this could not be correlated with the extent of metastases which is in contradistinction to patients with other solid tumours (Schellhammer *et al.*, in press). Experimental data from the mouse teratocarcinoma model also suggests that the role of the immune system with these tumours is complex. In the mouse tumour, the malignant stem cells, called embryonal carcinoma, are indistinguishable morphologically from germ cells. They carry a surface antigen, defined serologically, that is also present on mouse sperm and morula (Artzt *et al.*, 1973). These cells are the progenitors of the somatic cells of teratomas (Kleinsmith and Pierce, 1964) and when they differentiate, the antigen is no longer detectable but histocompatibility or H-2 antigens appear (Artzt and Jacob, 1974). The antigen seems to be expressed by an allele of a region on the 17th chromosome called the T-locus which is close to the H-2 complex (Artzt, Bennett and Jacob, 1974). This antigen is a true differentiation or foetal antigen. Theoretically, it should not normally be "seen" by the immune system which matures later in foetal development by which time the teratocarcinoma antigen has disappeared (Alexander, 1972). Therefore, it should behave as a foreign antigen to the host when it is re-expressed on tumour cells (Damjanor and Solter, 1974). Repeated immunisation is necessary to raise a detectable antisera titre so that it is a very weak system. To date these findings have not been extended to man, but they suggest that an immune response is possible to these tumours.

There is no good animal model for seminoma and it is unclear what the cell of origin of this tumour is. If it arises from the primary spermatocytes as suggested by ultrastructural studies (Pierce, 1966), it may possess different antigens from teratocarcinomas that are capable of eliciting a stronger immune response. The frequently-seen lymphocytic infiltrate in the stroma of the classical seminomas supports this and *in vitro* lymphocyte autochthonous tumour inhibition has been demonstrated by Hellström *et al.* (1971). As well, "blocking factors" have been eluted from a surgical seminoma specimen which abrogated *in vitro* cytotoxicity in an allogeneic combination (Sjögren *et al.*, 1972). Although 2 of our 6 patients had nodal hyperplasia, the other 4 were unremarkable. It is tempting to postulate that the excellent prognosis with seminoma is related to an immune response that it elicits.

At present the role of surgical ablation of lymph nodes regional to solid tumours is controversial. Some have suggested that this removes the first line of host defence to the tumour and is therefore contraindicated, whereas others believe that complete excision of the disease and therefore cure, requires removal of possible metastases in the regional lymph nodes. Further study of their role will help to resolve this problem in cancer surgery.

Summary

The role of the regional lymph nodes in cancer is controversial. Non-neoplastic changes in lymph node histology can be correlated with prognosis for some tumour types and reactivity has been interpreted as evidence of an immune response to the tumour. Attempts to correlate the patterns of retroperitoneal lymph node activity with prognosis in patients with seminoma and non-seminoma germinal testicular tumours have not been successful. The implications of these findings are discussed.

Figure 1D was photographed by N. Berlinger and V. Tsakraklides and was kindly provided by N. Berlinger.

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The Authors

M. A. S. Jewett, MD, Visiting Research Fellow and recipient of an Ontario Ministry of Health Fellowship.
S. I. Hajdu, MD, Attending Pathologist, Memorial Hospital.
R. A. Good, MD, PhD, President and Director, Sloan-Kettering Institute.
W. F. Whitmore, Jr, MD, Chief, Urology Service, Department of Surgery, Memorial Hospital.

Request for reprints to: W. F. Whitmore, Jr, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue,
New York, New York 10021, USA

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Book Reviews

Contributions to Nephrology: Current Research in Nephrology in Japan. Volume Editor—Y. UEDA, Tokyo. Series Editors—G. M. BERLYNE, Brooklyn, N.Y., and S. GIOVANNETTI, Pisa. Publisher—S. Karger. 60 figures and 24 tables. Sw. Fr. 49.

Many readers of the *British Journal of Urology* will have access to *Nephron* by personal subscription or through their libraries. Unfortunately this will not bring them the new series of Symposia issues by the same team but published separately as "Contributions to Nephrology". The first of these on proteinuria, appeared at the end of 1975, volumes II and III on glomerulonephritis and renal vascular hypertension in 1976 and this latest number at the beginning of 1977. They are expensive—about £11 to £16—so few libraries and fewer individuals in this country will order them automatically. Readers of *Nephron* are therefore well advised to look at publishers' advertisements for these monographs when they open their copy of *Nephron* and select them individually.

This collection of papers from Japan will have only limited appeal to urologists since the major topic is glomerulonephritis. There is one paper on bacteriuria over a ten-year period in the Yusaka University Hospital but almost every other contribution is associated with nephritis whether primary, secondary to lupus nephritis, or associated with Schönlein-Henoch syndrome. The traditional Japanese interest in experimental (Masugi) nephritis is well represented and there is a very useful study of the selectivity index as a predictor of response to treatment in nephrotic syndrome. This confirms the widespread impression that the present tests are poor predictors but holds out hope that they can be improved. There are descriptions of large series of patients with IgA glomerulonephritis and the closely related nephritis Schönlein-Henoch syndrome in childhood. With its large population and advanced medicine Japan must surely lead the field in such studies of natural history of disease. There is one more valiant attempt to classify the unclassified residue of proliferative glomerulonephritis in order to aid prognosis. It is based on a very large series but I doubt if it represents the last word.

Japanese nephrology is larger, and growing faster, than the same specialty in any Western country. Within a few years I expect Japanese articles to dominate our journals as their electronic calculators currently dominate our supermarkets. This is not a cheap introduction to Japanese nephrology but few of us can afford to go to Tokyo and it is time we learnt what was going on at the other side of the world.

D. N. S. K.

The Pathology of the Testis. Edited by R. C. B. PUGH. Pp. 487. Oxford: Blackwell Scientific Publications, 1976. Price £18·00.

Histological diagnosis depends on a combination of exact observation and subjective interpretation. In common diseases every pathologist can gain sufficient experience to make confident and accurate diagnoses, although differences of nomenclature and emphasis will provide material for the clinical pastime of detecting pathological inconsistencies. This is a useful pursuit, stimulating the histopathologist to keep abreast with modern developments, and ensuring that the clinician reads the entire report including the conditional clauses. In relatively rare disorders, such as tumours of the testis it is difficult for most pathologists to accumulate adequate experience, and errors occur. The Testicular Tumour Panel and Registry was set up in 1958 and by 1964 had accumulated sufficient material to publish a monograph (Collins and Pugh, 1964) which has remained a major reference text of histopathologists and oncologists for over a decade.

The present volume contains an extensive follow-up and expansion of the original work. It is the chapters on testicular tumours (Pugh), seminoma (Thackray and Crane), teratoma (Pugh and Cameron), combined tumours (Pugh), miscellaneous tumours of epithelial type (Brown), and paratesticular tumours (Gowing) that many will explore first. The gross illustrations and micrographs are large and of uniformly high standard. The classification of teratomas has been simplified, and there is a valuable discussion of the relationship to other systems of nomenclature. The division of the Malignant Teratoma Intermediate Group (MTI) into sub-groups; MTIA and MTIB, depending on the presence or absence of differentiated structures, has been replaced by a single group, Malignant Teratoma Undifferentiated (MTU) consisting of the old MTA and MTIB groups and MTIA has now been replaced by MTI. This fusion of histologically separable groups follows the demonstration of similar survival after orchidectomy and radiotherapy. This evolution of histological classification in response to natural history and therapeutic response is an excellent example to pathologists wishing to ensure that their observations remain clinically germane.

But this is not only a book for histologists; in addition to a chapter on clinical management, urologists and oncologists will find much data on the survival and the response to treatment of the testicular tumours. The decision to expand beyond the strict boundaries of tumour pathology will be widely welcomed. The chapter on structures, function and development (Neville and Grigor) is particularly well prepared. A chapter on the inflammatory conditions of the testis (Morgan) is a useful addition since the differentiation of these conditions from tumour is not always simple.

There is little to criticise in the format or production of this book which will become a mandatory acquisition for all those concerned with the pathology of the testis. Even at a cost of £18·00 this is an investment well worth acquiring.

A. R. M.

Urologic Radiology. By MARCY L. SUSSMAN and ALEX NEWMAN. Second edition. Pp. vii+518 with 482 illustrations. Baltimore: Williams & Wilkins, 1976. $45.

There are now several books on radiology of urological diseases. Unfortunately this one has little to recommend it in such a competitive field. 2 points in its favour; it contains numerous references—ancient and modern—and has a section on isotope techniques. Isotopes are obviously one of the authors' special interests. Unfortunately, even this subject is not dealt with very well. A confusing array of isotopes is paraded before the reader with little attempt to provide any useful evaluation. Ultrasound, which is probably more valuable in urology, is dealt with more briefly.

The text is rambling, repetitive and in parts incomprehensible. There are many inaccuracies; we are told that females have no external sphincter of striated muscle and cystinuria is confused with homocystinuria. Papillary necrosis is said to be a special instance of chronic pyelonephritis, and what is to be made of statements such as "renal angiography is of little value in the diagnosis of calculus" and "air bubbles are transparent whereas calculi are translucent".

The descriptions of investigatory procedures are often cursory or unhelpful. It is difficult enough to get patient co-operation in voiding cystography without suggesting that it should be done in the Trendelenburg position. Probably the worst feature of the book is that the headings are often totally misleading. For example, chyluria is dealt with under the heading of retrograde pyelography and presacral tumours under tumours of the kidney.

The illustrations are generally reasonable but some could be omitted altogether. The captions are occasionally at variance with the text or missing completely.

Before the next edition is produced a lot of editing and revision is needed.

W. S.

Clinical Aspects of Uremia and Dialysis. Edited by S. G. MASSRY and A. L. SELLERS. First edition. Pp. 746. Springfield: Thomas, 1976. $59.75 (about £35).

That there has been a glut of textbooks on renal medicine must be particularly obvious to readers of a urological journal which publishes them. There have been some good ones but rarely have I been able to say in these columns "This book satisfies a long-felt need". Massry and Sellers is one exception. There have been only 2 shortish English textbooks on dialysis in the last decade and the more numerous ones in German have not been translated. This is the most comprehensive text in any language, to my knowledge, and will be an indispensable reference book for renal libraries.

The authorship is almost exclusively American with a single Swiss contributor and three-quarters of the authors are from the West Coast. No doubt their proximity to the editors' phone explains why all the reference lists are complete to about the same time (1973) though it is a pity that this achievement is marred by a 3-year gap between writing and publication. Many of the names are well known and inevitably linked with their subject. Eschbach writes on anaemia; Massry and Coburn on bone disease; Teschan and Ginn on CNS complications; Levy on psychological problems; Weidmann and Maxwell on hypertension; Bischel on hepatitis; Bagdade on hyperlipidemia; Fine, Korsch and Grushkin on dialysis in children. There are excellent descriptions of shunts and fistulae, of nutritional requirements and, for those with a mathematical turn of mind, a thorough description of solute transport and ultrafiltration by Gotch. All the major complications of dialysis receive a chapter or at least a section and there is a guide (briefer than I would have wished) to drug therapy in renal failure. The sections on equipment and alternative treatments (peritoneal dialysis, sorbents etc.) are relatively short and this is not, in any sense, an instruction manual on haemodialysis for the tyro. Rightly or wrongly, the editors have left the practical details to shorter and handier books like Wing and Macgowan. However, I expect to see Massry and Sellers on the shelves of many dialysis units as the fastest short-cut to the original literature. It may seem expensive but with some disposable dialysers now costing £40 its price is a reasonable investment.

D. N. S. K.

Pediatric Nephrology. Volume 2. Epidemiology, Evaluation and Therapy. Edited by J. STRAUSS. First edition. Pp. 582. New York: Stratton International, 1975. $19.95.

This is the second in a series of books based on a postgraduate course ("international forum for exchange of ideas and experience") given annually by the Division of Pediatric Nephrology of the University of Miami. Readers should not be put off by this description nor by the references in the introduction to Renee Habib as "France's factual fireball" and Mrs Strauss as "a wonderful human being". Most of the writing is much better and indeed very attractive. The discussions have been preserved after each group of papers and are well edited. The descriptions are brief—typically about 10 pages with 40 references—and can be read at a sitting over breakfast or in the train. With 36 subjects covered, there is quite a choice for the urologist as well as the nephrologist—an informative chapter on urinalysis (although it perpetuates some myths about the origin of casts), and descriptions of urinary infection, uric acid nephropathy, enuresis, cystinosis, renal tubular disorders, uraemia, shunt and fistula surgery, renal transplantation, and haemodialysis in children. The more adventurous urologist could even explore the chapter on psychosocial aspects of dialysis and transplants in children; it is a subject which usually makes me turn the page as quickly as possible but this is better than most discussions and contains an evocative portrait of the internal anatomy (consisting entirely of kidneys and blood vessels) by a child recipient of a transplant.

Most conference proceedings, however they are disguised, are ephemeral and not a worthwhile investment for the individual clinician (except as an aide-mémoire if he attended). This will be no exception but if your library is well endowed and can afford it, it is worth borrowing for a good browse.

D. N. S. K.

Urolithiasis Research. Edited by H. FLEISCH, W. G. ROBERTSON, L. H. SMITH and W. VAHLENSIECK. Pp. 582, well illustrated. New York: Plenum Press, 1977. $54.00.

This book is the proceedings of an international symposium on urolithiasis research held in April 1976. The publication of typescripts as submitted has allowed early publication although it has not apparently kept the price down.

Despite rather poor quality paper the photographic illustrations are of excellent quality. The first 230 pages are devoted to reviews of various aspects of renal physiology relevant to stone formation and to the treatment of renal stones.

The list of authors includes leaders in the field of calcium metabolism, renal physiology and nephrology. Their reviews consist largely of reports of their own work in the field backed up in most cases by a comprehensive review of the literature. These papers are well illustrated and easy to read and will provide a valuable source of reference for those involved in research or clinical management of patients with renal stones.

The last 350 pages of the book are devoted to original papers (presented as papers at the Symposium); these cover a very wide range of subjects and vary from balance studies to clinical case reports. This section of the book will be of particular value to those engaged in clinical or laboratory research.

The book can be recommended to all departments of urology, nephrology and physiology as an up-to-date and comprehensive reference on all aspects of renal stone formation.

R. W.

Kidney and Urinary Tract Physiology II. Edited by KLAUS THURAU, (International Review of Physiology, Vol. II.) Pp. 326, well illustrated. Baltimore: University Park Press, 1977. £17·50.

The editor explains the misleading title of this excellent book in the preface. There have apparently been insufficient advances in our knowledge of the physiology of the urinary tract to warrant a chapter on this subject.

If we accept this and assess the book as a review of some aspects of renal physiology then it performs well. The work reviewed is largely that up to the end of 1974 although some work from 1975 is included so that for a text book there has been remarkably little delay in publication. There are chapters reviewing renal blood flow, prostaglandins, renin, tubular transport, renal handling of calcium, phosphate and urate and ammonia production and excretion.

There is inevitably some repetition since renin has to be mentioned in discussing renal blood flow and prostaglandins as well as in its own chapter but the overlap is not too extensive. The reviewers in general include reference to their own work. Dr Tobian builds the whole review around his own work to provide a very readable chapter although perhaps at the cost of a slightly less extensive review of the literature than that given in other chapters.

The book is also enhanced by guides to the subject matter at the beginning of many chapters together with a liberal use of sub-headings so that answers to questions can be quickly found. Frequent summaries of conflicting evidence by the authors are helpful and also tend to personalise the review.

This book is aimed largely at the renal physiologist and nephrologist; for those with a special interest in the subjects covered a personal copy would be of value but at £17·50 it will usually be a library purchase.

R. W.

Conferences and Courses

Medical Oncology Society

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Nice, 4th to 6th December 1977

This Congress is open to all oncologists. It will deal with clinical and experimental aspects of cancers, new methods of exploration, treatments, especially chemotherapy and immunotherapy and strategy.

For further information and registration, write to: M. Schneider, Centre Antoine Lacassagne, 36 Voie-Romaine, 06054 Nice Cedex, France. Tel.: (93) 80.54.23 Ext: 248; Telex: Cal Nice 470 344 F.

Biennial Congress of the South African Urological Association

This congress will take place in Cape Town from 17th to 22nd September 1978.

For further particulars please contact: The Secretary, South African Urological Association, 831 Medipark, Hertzog Boulevard, Cape Town, 8001, South Africa.

Liverpool University and Liverpool Regional Urological Centre

A week's course in *Special Aspects of Urology* will be held from 11th to 17th December 1977.

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Further information about the course is obtainable from: Mr N. O. K. Gibbon, c/o Postgraduate Office, Faculty of Medicine, P.O. Box 147, Liverpool L69 3BX.

Leadbetter Symposium on Genitourinary Oncology

The first biannual Leadbetter Symposium on Genitourinary Oncology will be held in the West Bank Auditorium of the University of Minnesota, Minneapolis, from 8th to 10th September 1977.

Full details are obtainable from: The Registrar, Continuing Medical Education, Box 293, Mayo Memorial Building, 420 Delaware Street S.E., University of Minnesota, Minneapolis, Minnesota 55455, U.S.A.

50th Congress of the Italian Urological Society

The 50th Congress of the Italian Urological Society will be held in Ancona, Italy, from 12th to 14th September 1977, under the Presidency of Mr. F. Bianchi.

Main topics: Isolated hematuria; Intra-operative hypothermia and bench surgery of the kidney.

Further details may be obtained from Mr Bianchi, Ospedale Regionale, Ancona, Italy.

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Bilirubin	0·1–0·8	mg/100 ml	17	0·059	2–14	μmol/l
Calcium	8·6–10·5	mg/100 ml	0·25	4	2·15–2·65	mmol/l
Chloride	100–107	mEq/l	1	1	100–107	mmol/l
Cholesterol	140–240	mg/100 ml	0·026	38·5	4·0–6·5	mmol/l
Creatinine	0·6–1·4	mg/100 ml	88	0·0114	55–125	μmol/l
Glucose	65–95	mg/100 ml	0·056	18	3·5–5·5	mmol/l
Iron	110–130	μg/100 ml	0·18	5·6	circa 20	μmol/l
Magnesium	1·4–1·8	mEq/l	0·5	2	0·70–0·90	mmol/l
Phosphate	2·5–4·5	mg/100 ml	0·32	3·1	0·8–1·4	mmol/l
Potassium	3·8–5·2	mEq/l	1	1	3·8–5·2	mmol/l
Protein (total)	6·5–8·0	g/100 ml	10	0·1	65–80	g/l
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IgG	500–1600	mg/100 ml	0·01	100	5·0–16·0	g/l
IgA	125–425	mg/100 ml	0·01	100	1·25–4·25	g/l
IgM	50–180	mg/100 ml	0·01	100	0·5–1·8	g/l
Sodium	136–149	mEq/l	1	1	136–149	mmol/l
Transferrin	150–300	mg/100 ml	0·01	100	1·5–3·0	g/l
Triglyceride	60–140	mg/100 ml	0·0113	88·5	M2·0 P<1·5	mmol/l
Uric Acid	2–7	mg/100 ml	0·06	16·7	0·1–0·4	mmol/l
Urea	15–40	mg/100 ml	0·17	6·0	2·5–6·5	mmol/l
Arterial Blood						
Base Excess	−3–+3	mEq/l	1	1	−3–+3	mmol/l
PCO_2	32–46	mm Hg	0·135	7·5	4·5–6·0	kPa
PO_2	80–100	mm Hg	0·133	7·5	10·5–13·5	kPa
Urine Outputs/24 hr						
Calcium	200	mg	0·025	40	5	mmol
Creatinine	1–2	g	8·8	0·113	9–18	mmol
5HIAA	3–17	mg	5·23	0·19	16–90	μmol
Inorganic P.	1000	mg	0·032	31	30	mmol
Magnesium	100	mg	0·041	24	4·2	mmol
Potassium	70	mEq	1	1	70	mmol
Protein	<0·05	g	1	1	<0·05	g
Sodium	200	mEq	1	1	200	mmol
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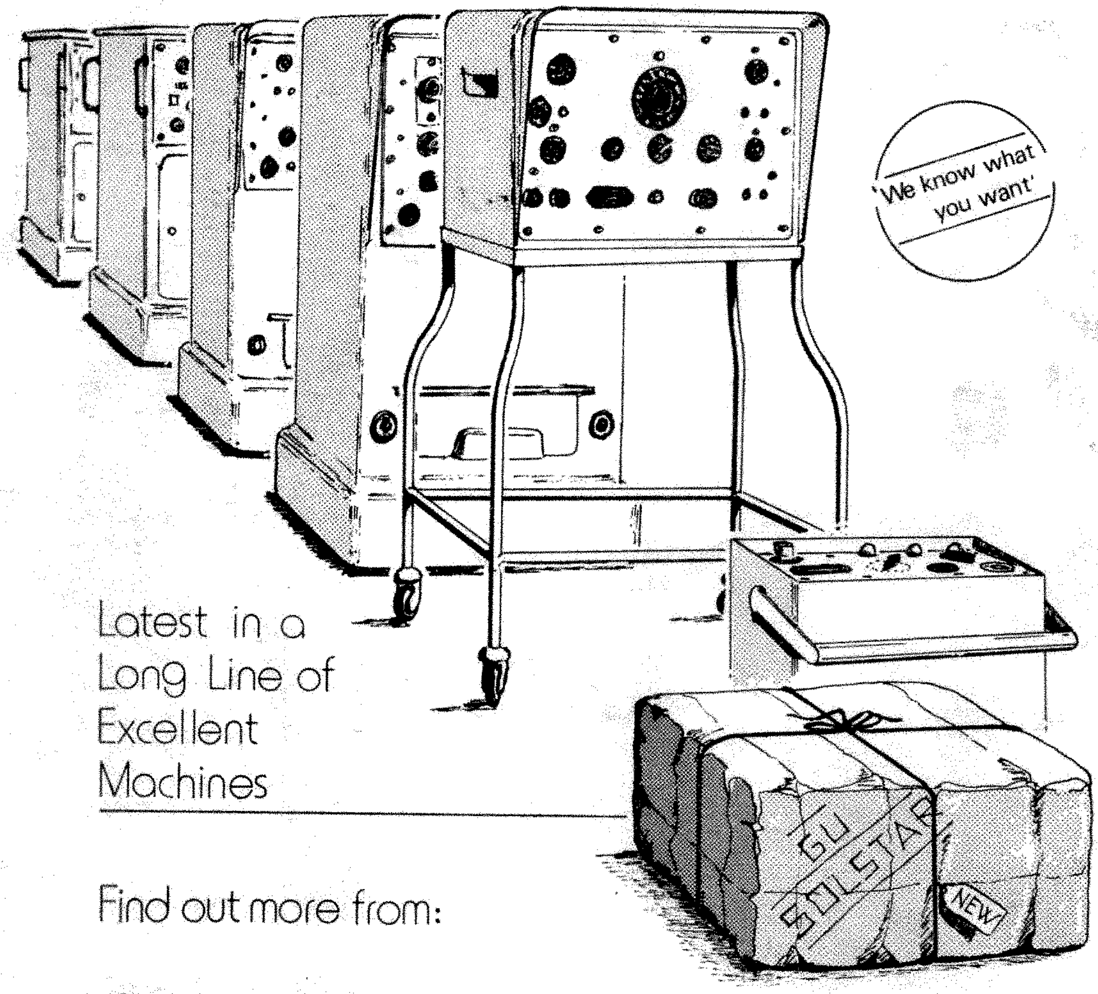
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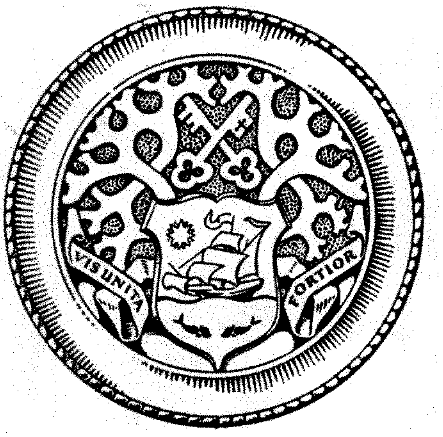

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BAUS Annual Meeting 1978

On page 565 of this issue of *B. J. Urology* the date for submitting Abstracts of Papers to The British Association of Urological Surgeons is 1st December 1977. This date has now been revised to 20th January 1978.

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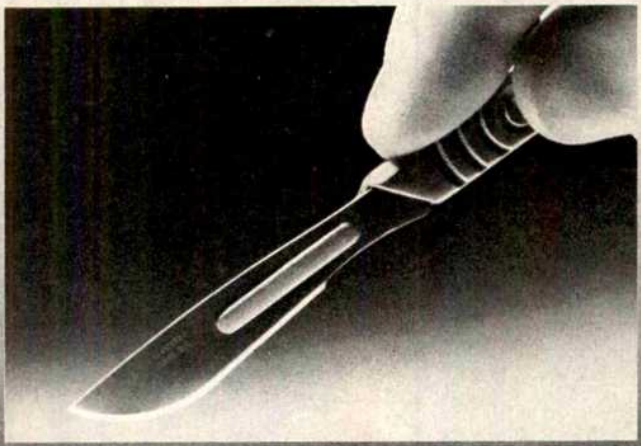

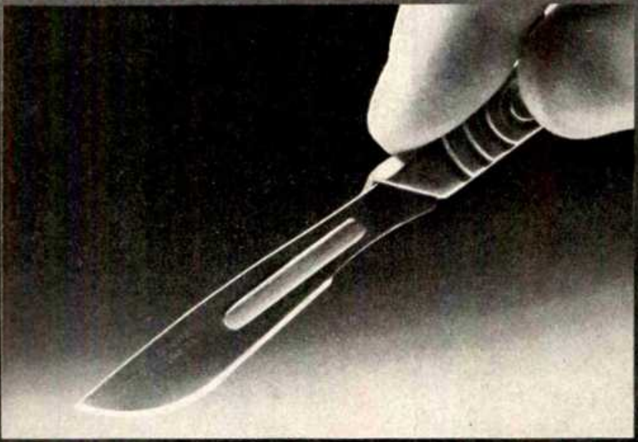

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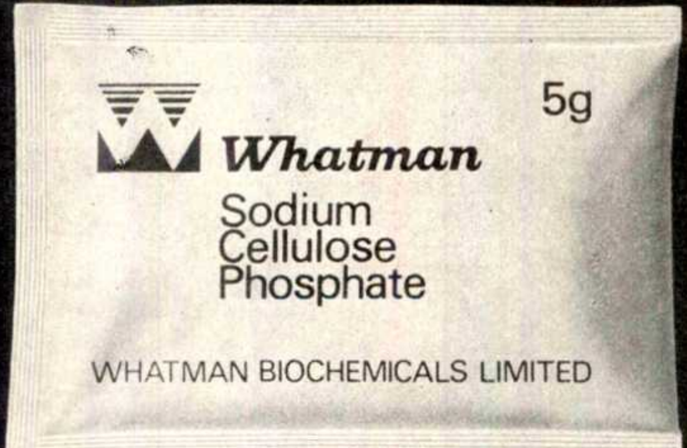

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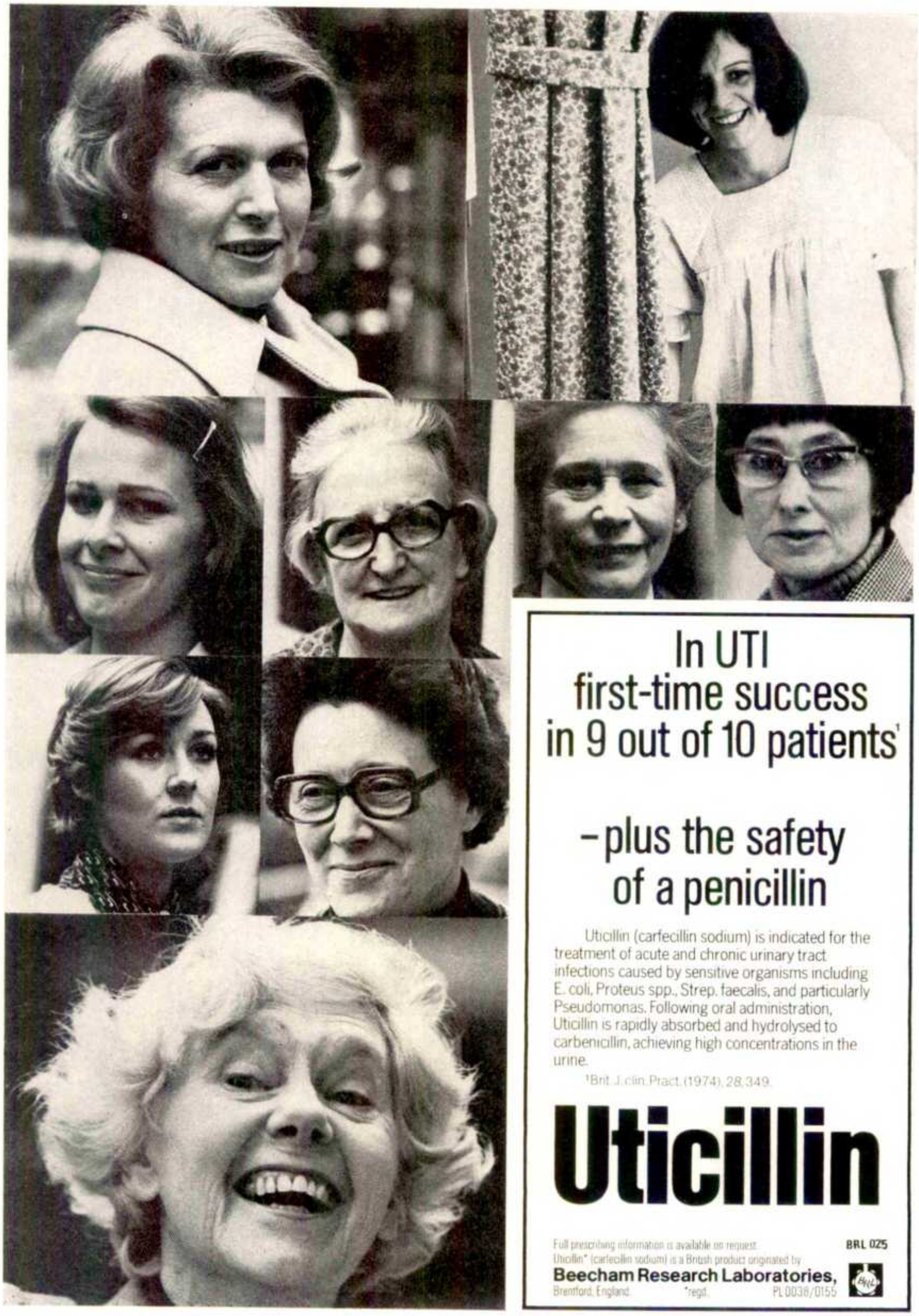

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The award will be announced at the June meeting of the Association.

Continued on page vi

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Brief reports (preferably with 1 and not more than 2 illustrations) of unusual cases not published elsewhere may be submitted as summaries of not more than 200 words for consideration for publication as Single Case Reports. They should comprise (1) a Title, (2) Case description and (3) a brief Comment. The authors and references are each limited to 3. The titles of these reports will usually be recorded in Index Medicus and by MEDLARS.

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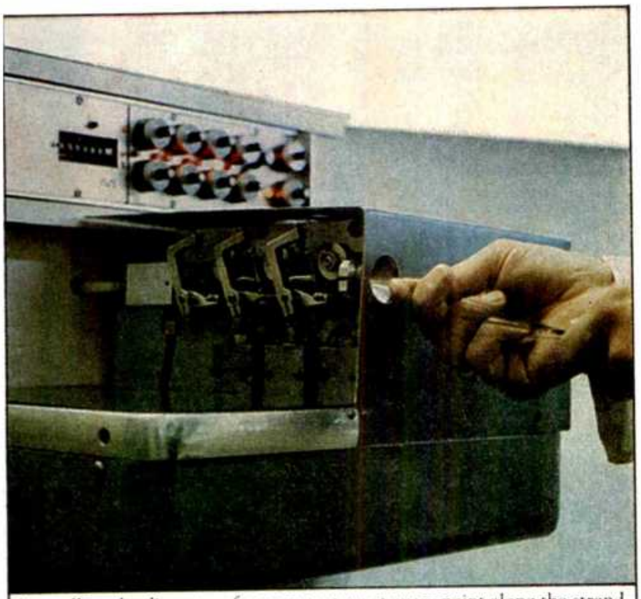
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Tuberose Sclerosis and Bilateral Renal Carcinoma

R. J. HONEY and R. M. HONEY

St Thomas' Hospital, London; and Salisbury Central Hospital, Salisbury, Rhodesia

(Received 25 May 1977; accepted for publication 14 June 1977)

Tuberose sclerosis is a hereditary disease showing a widespread disturbance of organogenesis affecting many parts of the body. It is chronically progressive and usually manifests itself before 18 years of age. The incidence has been estimated at 1 per 150,000 of the population in England (Dawson, 1954) and cases have been recorded in a number of other races with similar incidences (Singer, 1971). In the most severe form, sometimes called epiloia, patients show the classical triad of retarded mental development, epilepsy and "adenoma sebaceum" of the face. Many patients, however, exhibit incomplete forms of the disease ("formes frustes") in which many of the characteristic abnormalities are absent. Dawson (1954) holds that the incomplete form is as common as the major form and Lagos and Gomez (1967) found that 38% of their patients were of normal intelligence.

Case Report

Miss P. C., a white girl aged 18, presented in April 1969 complaining of pain in the right iliac fossa on exercise for 6 months. She had no past medical history of note and had never suffered convulsions. She was a healthy looking girl of average intelligence. Abdominal examination revealed a large mobile mass in the lower pole of the right kidney. A nodular area of thickened skin, 10 cm in diameter, was noted over the right loin (Fig. 1), and fibrous nodules were found under the nail-fold of her right ring finger (Fig. 2) and right third toe. Her haemoglobin and blood urea were within normal limits and there was no abnormality found in her urine. An intravenous pyelogram (Fig. 3) demonstrated a space-occupying lesion containing a small amount of stippled calcification in the lower pole of the right kidney. The left kidney appeared normal.

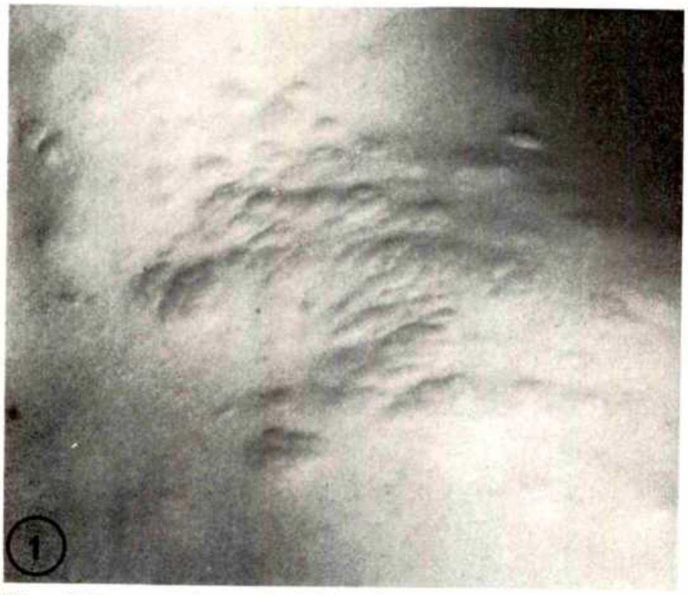


Fig. 1. Shagreen patch over the right lumbar region.

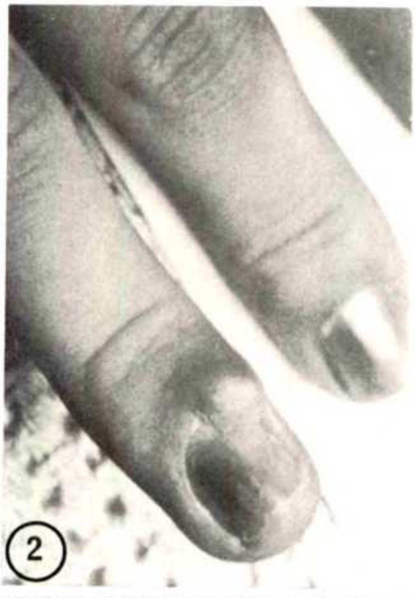
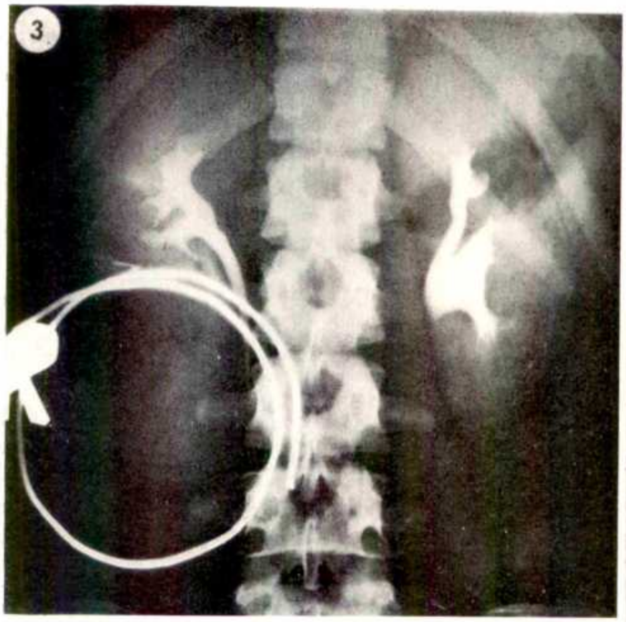


Fig. 2. Periungual fibroma on the right ring finger.



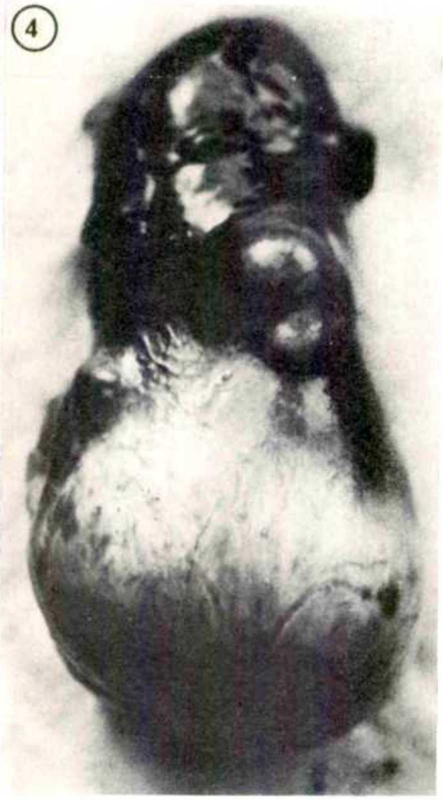
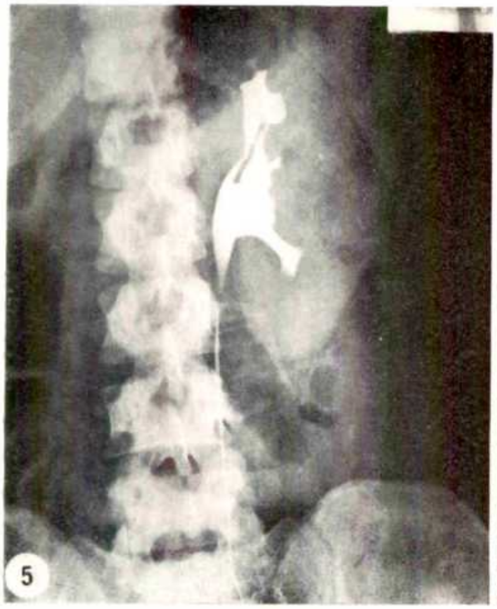


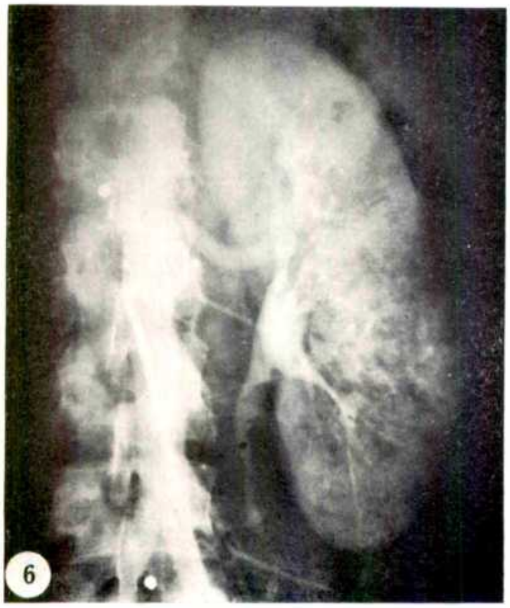
Fig. 3. Intravenous pyelogram, 1969.

Fig. 4. Right nephrectomy specimen.

Fig. 5. Left retrograde pyelogram, 1972.

Fig. 6. Left renal arteriogram, 1972.





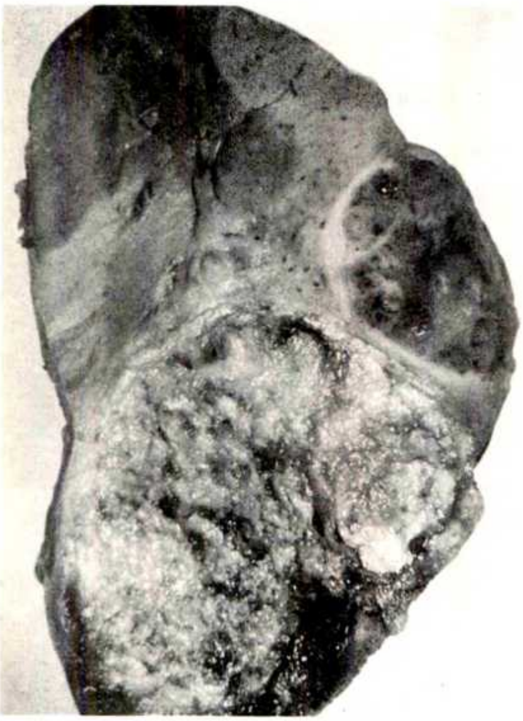


Fig. 7. Partial nephrectomy specimen from the left kidney.

The right kidney was explored and a mixed solid and cystic tumour was found occupying its lower two-thirds. A radical nephrectomy was performed (Fig. 4). Histological examination showed renal carcinoma of mixed architecture, the majority being of a papillary type (Fig. 8) with few mitotic figures, but there were also areas of solid clear cell carcinoma (Fig. 9). It was not possible to say whether the two types of growth represented two separate primary tumours.

Following nephrectomy the patient made an uneventful recovery and did not return for follow-up until February 1972, when she was referred with a history of haematuria for 48 hours, followed by anuria for 30 hours. After drainage of the left kidney by ureteric catheterisation intravenous pyelography showed distortion of the lower and middle calcyes not present in the previous intravenous pyelogram. This was confirmed by retrograde pyelography (Fig. 5). An arteriogram (Fig. 6) demonstrated an abnormal vascular supply with "puddling" of contrast in the venous phase, characteristic of hypernephroma. No aneurysmal dilatations, a feature of angiomyolipoma (Sood, Mancini and Kropp, 1975; Bissada *et al.*, 1975), were seen.

Exploration of the left kidney revealed 3 tumours in the lower pole, and a partial nephrectomy was performed (Fig. 7). Histological examination of the tumours showed them to be largely composed of renal carcinoma growing in papillary fashion (Fig. 10). There was no way of telling on histological grounds whether these were further primary tumours or secondaries. In sections of both kidneys there was an abnormally large quantity of smooth muscle, not apparently related to the pelvis or calyces, nor to blood vessels (Fig. 11). This muscle may be of hamartomatous origin (Inglis, 1960).

She recovered well from the second operation, and 5 years later she is symptom free, with a serum urea of 6·8 moles per litre, and a creatinine clearance of 61·7 ml/min.

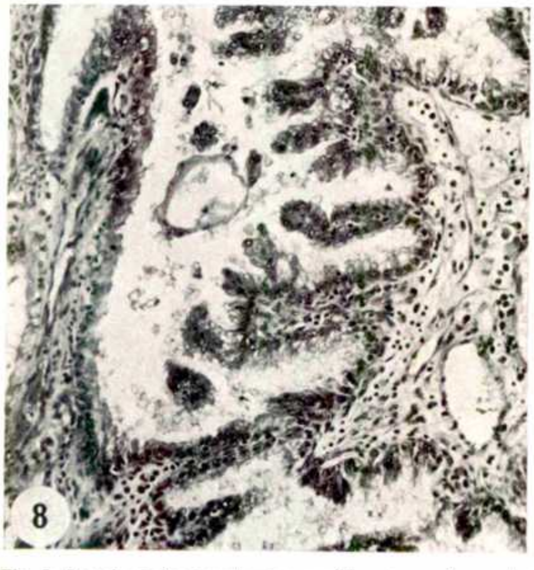
It was not until the patient presented with multiple tumours of her second kidney that the significance of the periungual fibromata and the shagreen patch on her loin were appreciated, and the diagnosis of tuberose sclerosis made. A subsequent examination revealed cosmetically well-disguised adenoma sebaceum of the face and a number of achromatic patches of skin on the left leg. Fundoscopic examination was normal.

An X-ray of the skull demonstrated multiple sclerotic areas in an abnormally thick calvarium, but no intracranial calcification was demonstrated. Similar discrete round and oval areas were also present in both iliac bones (Fig. 15). An X-ray of the hands showed the typical picture of multiple small cysts in the phalanges. X-rays of the chest were normal. All other members of her family, her parents and 2 brothers, are free from any detectable features of the disease.

Discussion

The diagnosis of tuberose sclerosis when florid presents no problem, but because of the various manifestations which may be present in any number or combination, the correct diagnosis is often overlooked in the first instance. The following features are characteristic of the disease: (1) A family history. (2) Cerebral involvement: sclerotic glial nodules, or tubers, develop in the basal ganglia and periventricular regions resulting in retarded mental development and epilepsy. Skull X-rays may demonstrate circumscribed intracranial calcification and electroencephalographic findings are abnormal in about 70% of cases (Lagos and Gomez 1967). (3) Retinal lesions: phacomata (flat tumours), which are local proliferation of glial tissue. (4) Cutaneous lesions: (*a*) "Adenoma sebaceum", which are actually angiofibromas, in a butterfly distribution on the cheeks and nose. (*b*) "The shagreen patch", a thickened nodular area of skin most commonly seen over the lumbar region. (*c*) Areas of hyperpigmentation or achromatic patches. (*d*) Café au lait spots. (*e*) Periungual or subungual fibromas. (5) Multiple visceral tumours: these are usually hamartomatous malformations rather than neoplasms, and may be found in the kidneys, heart, liver, adrenals, thyroid, lungs and ovaries. The most common site is the kidney, where they are usually multiple and bilateral (Golgi, 1961; Chonko *et al.*, 1974). (6) Pulmonary involvement: multiple cystic lesions giving a honey-combed appearance, or intrapulmonary hamartomata (Hawkins, 1959). (7) Skeletal lesions: sclerotic islands may be seen in the skull and pelvic bones, or cystic lesions in the phalanges (Beck and Case Hammond, 1857). These are asymptomatic and are purely of diagnostic interest. (8) Stigmata common among mentally defective patients: the simian hand, hypertrophy or asymmetry of the ears, high arched palate, supernumerary digits, or shortening and incurving of the little finger (Critchley and Earl, 1932).

There has been debate as to the exact mode of transmission from parent to offspring (Gunter and Penrose, 1935; Nevin and Pearce, 1968); however, it appears that the disease is inherited as an autosomal dominant condition. It has been suggested by Bundey (1971) that because of the great reduction in biological fitness of these patients as many as 80% of new cases probably occur as a result of new mutations.



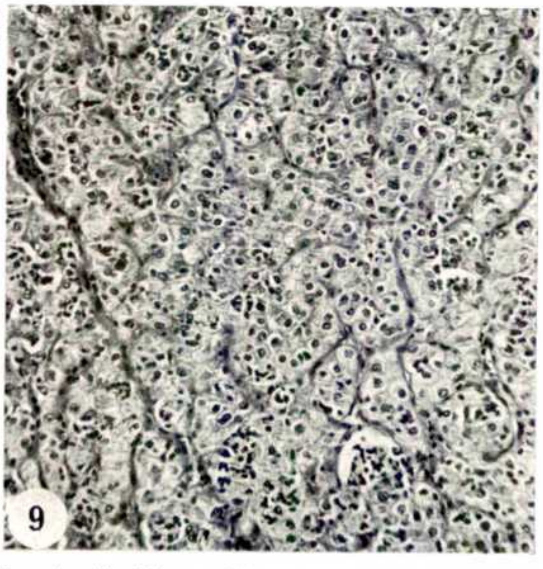


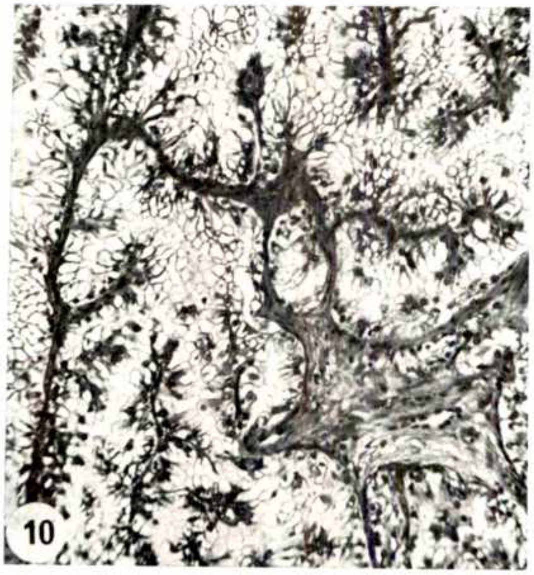
Fig. 8. Renal carcinoma showing papillary type of growth, from the right kidney. × 200.

Fig. 9. Renal carcinoma showing solid clear cell type of growth, from the right kidney. × 200.

The incidence of renal tumours, in most cases angiomyolipomas, in tuberose sclerosis is undoubtedly high, and it may well be as high as the 80% reported by Hyman in 1922. The difficulty in estimating the incidence more exactly lies in the inadequacy of pyelography in demonstrating some of the smaller tumours during life. However, with the more modern techniques of nephrotomography and radionuclide imaging studies (Blatt, Hayt and Freeman, 1974) these smaller tumours may be more readily demonstrated. Angiomyolipomas are generally considered to be hamartomatous malformations (Moolten, 1942) although the mesothelial elements often have a primitive appearance and occasionally show sufficient pleomorphism to look malignant. However, although appearing malignant they invariably remain localised to the kidney.

Cases of renal carcinoma (hypernephroma) in tuberose sclerosis are rare, occurring only in the earlier literature (Pellizzi, 1900, 1901; de Montet, 1908; Marcuse, 1909; Bonfigli, 1910; Hyman, 1922), and some people have doubted their existence (Mertz, 1942). The most recent of the above cases, however, was of a boy aged 10 from whom a kidney 3 times its normal size was resected. The tumour was reported to be a "hypernephroma", but the child remained in excellent physical condition with no evidence of recurrence 4 years later. Although the word "hypernephroma" was often used rather loosely, it is possible that the tumour in this case was similar to the tumours in our patient in that although it appeared to be a renal cell carcinoma histologically, its behaviour was more like the angiomyolipoma. The mode of behaviour of "hypernephromata" associated with tuberose sclerosis may therefore be unusual. The tumours resected from our patient were histologically indistinguishable from renal cell carcinoma, but her present condition suggests that, had they been left, they might have pursued a benign course.

As renal tumours in tuberose sclerosis are, almost without exception, hamartomata, treatment should be conservative, and operative intervention reserved for cases with uncontrollable haematuria, infection, pain, or where the symptoms produced are due to the size of the tumour. Percutaneous needle biopsy is not recommended because of the vascular nature of many of these tumours.



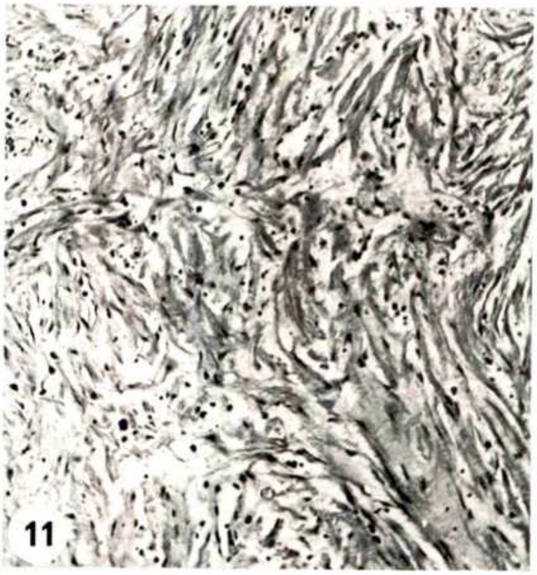


Fig. 10. Renal carcinoma showing papillary type of growth, from the left kidney. × 200.

Fig. 11. Stroma tissue from the medullary zone of the left kidney, showing excessive smooth muscle. × 200.

Summary

A case report is presented of an 18-year-old girl of normal intellect with tuberose sclerosis and multiple bilateral renal carcinomas. These tumours were successfully treated surgically by right nephrectomy and left partial nephrectomy.

The usual renal lesion in these patients is the angiomyolipoma, which is a hamartoma. Renal carcinoma associated with tuberose sclerosis is extremely rare, and the mode of behaviour of these tumours may be unusual.

We would like to thank Dr I. W. Whimster for his help in reviewing the histological sections.

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The Authors

R. J. Honey, FRCS, Surgical Registrar, St Thomas' Hospital, London.
R. M. Honey, OBE, MRCOG, FRCS(Ed), Consultant Urologist, Salisbury, Rhodesia.

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Renal Carcinoma presenting with Pulmonary Emboli: A Review of Two Cases

RICHARD L. LEVINE and RICHARD A. AIRHART

Department of Urology, Tulane University School of Medicine, New Orleans, Louisiana

(Received 9 March 1977; accepted for publication 13 June 1977)

Less than half of the number of patients with renal adenocarcinoma present with the classic triad of loin pain, flank mass and haematuria; the remainder appear in a myriad of ways.

We report two cases of renal carcinoma which presented with pulmonary emboli in a 6-month period.

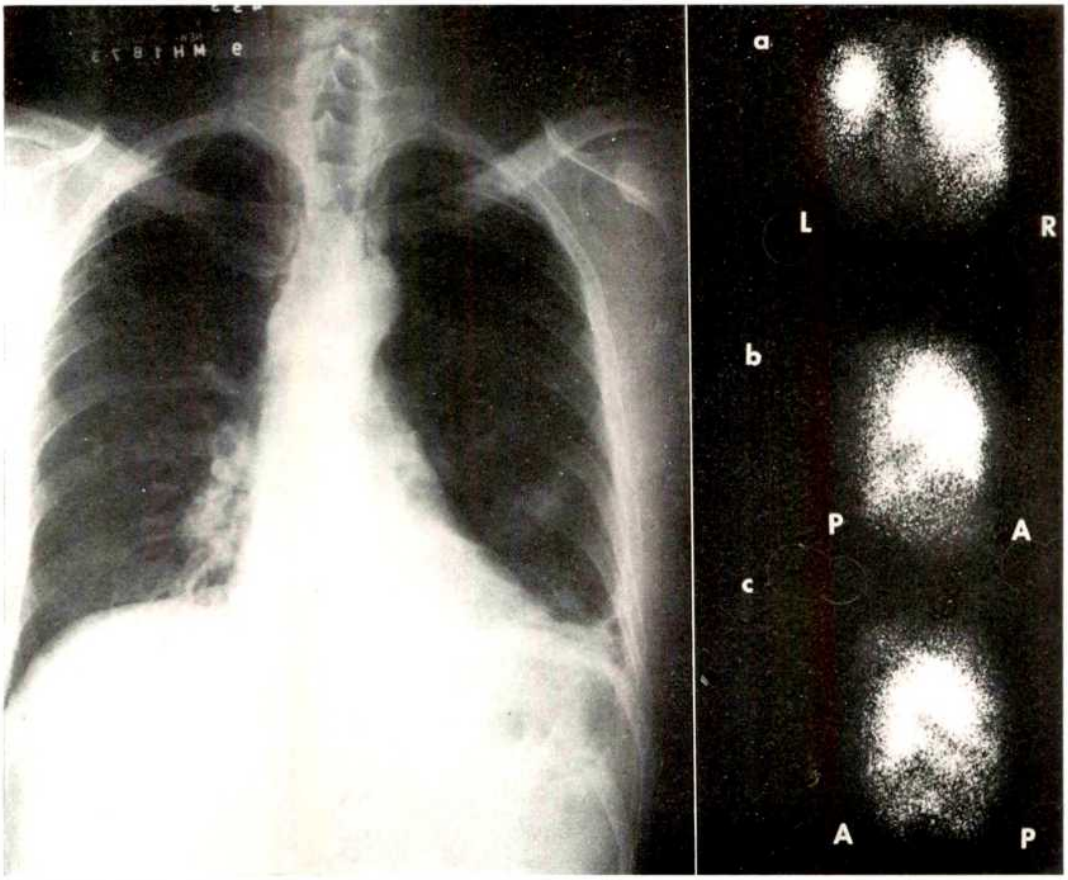

Fig. 1. Chest X-ray documents left costovertebral angle blunting. *a*, Posterior lung scan labelled left and right. *b*, Right lateral lung scan labelled posterior and anterior. *c*, Left lateral lung scan labelled anterior and posterior.

Case Reports

Case 1. A 50-year-old white male entered the hospital in August 1973 complaining of left chest pain. Physical examination revealed a well-developed man with a blood pressure of 150/90 mm Hg, pulse of 104 and respiration of 20. There was rigidity with poor movement of his left chest wall, with râles and dullness to percussion over the lower one-half of the left lung posteriorly. One day later he had haemoptysis. Laboratory studies, including urinalysis and haematologic studies, were unremarkable. Chest X-ray showed blunting of left-sided costovertebral angle. A lung scan revealed decreased vascular perfusion to both lower lobes, the left greater than the right (Fig. 1). Anticoagulants were begun, and the patient was discharged on coumarin. The coumarin was discontinued after 1 month.

He was readmitted 3 months later with left chest pain, palpitations and nausea. Physical examination again revealed rigidity with poor movement of the left chest wall and dullness of the left base. Laboratory studies were again unremarkable, and the chest X-ray showed a left lower lobe infiltrate. A lung scan was reported as unchanged (Fig. 2). The patient was again placed on heparin, but on his fourth day of treatment he complained of right flank pain and right lower quadrant abdominal pain. Abdominal X-rays showed obliteration of the right psoas margin. A diagnosis of retroperitoneal haematoma was made, and the heparin was discontinued. An intravenous pyelogram (IVP) showed an enlarged right kidney with suggestion of a right lower pole mass (Fig. 3). A urological consultation was obtained, and the tentative diagnosis was intracapsular haematoma, although tumour could not be ruled out. He was discharged on aspirin with an appointment for further urological evaluation in 1 month, but he failed to return.

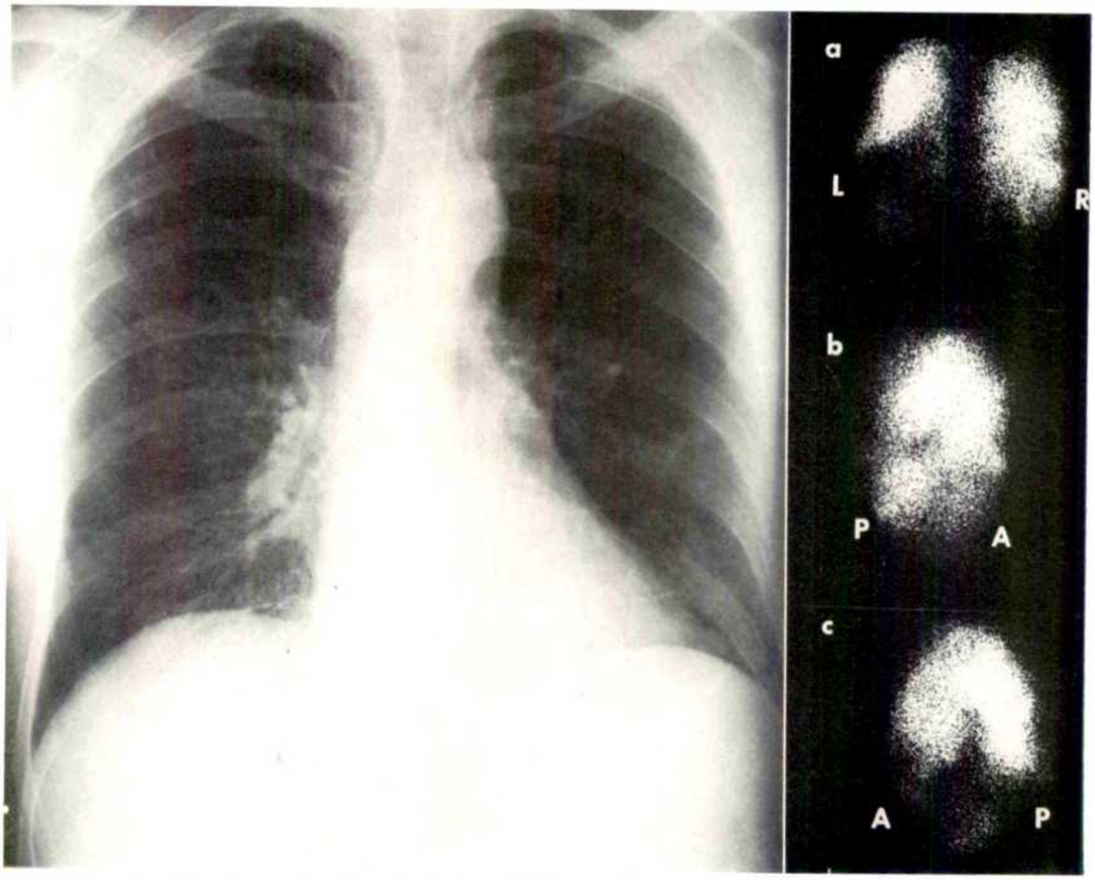

Fig. 2. Chest X-ray documents a left lower lobe infiltrate. Figs *a*, *b* and *c* are labelled as in Fig. 1.

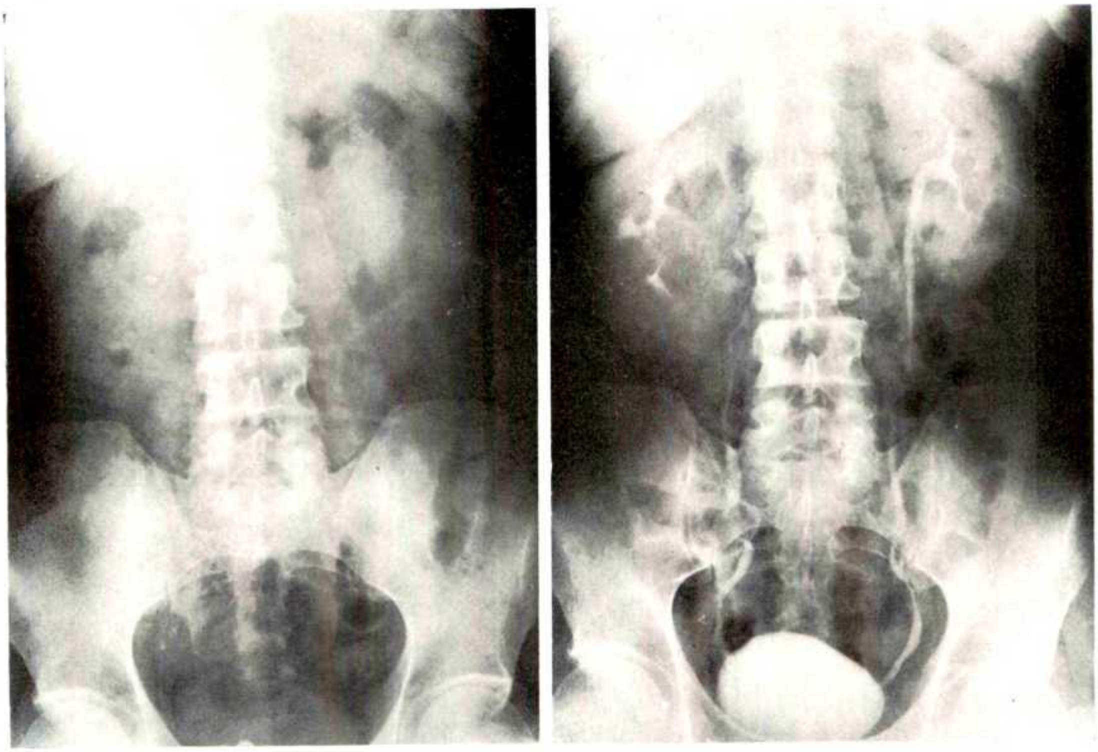

Fig. 3. Intravenous pyelogram (IVP) showing enlarged right kidney with suggestion of a right lower pole mass.

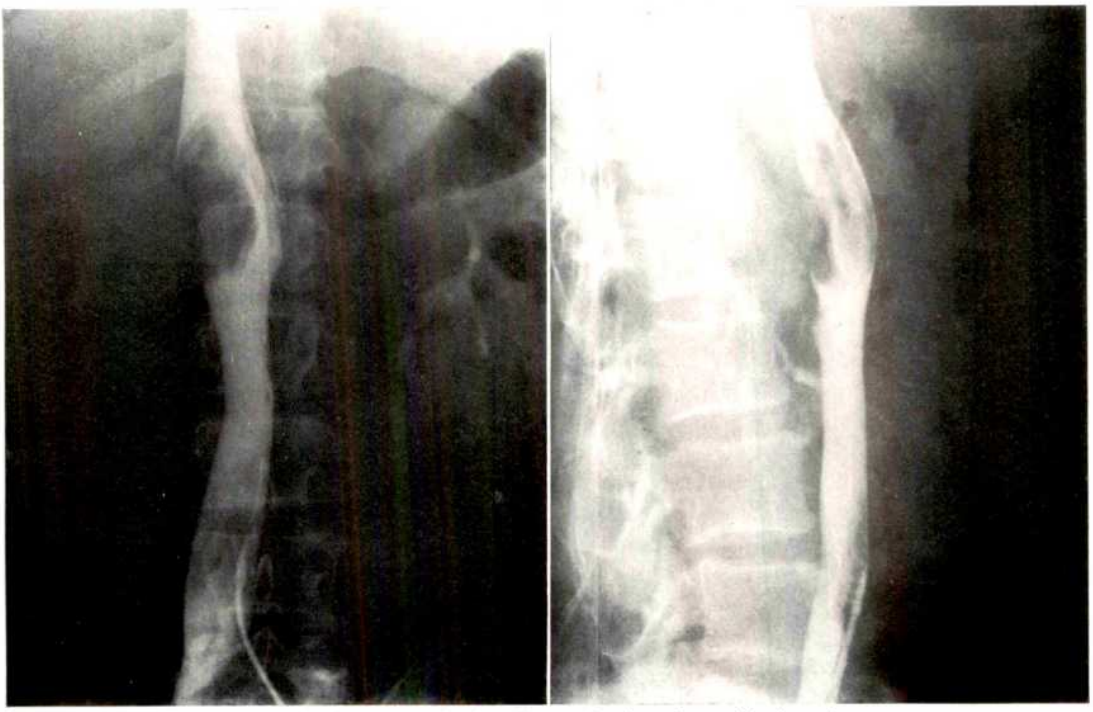

Fig. 4. Inferior vena cavogram showing tumour in the right renal vein and extending into the vena cava.

The patient was next admitted to the general surgical service in May 1974 with right flank pain and right upper quadrant abdominal pain. Laboratory studies were again normal. A cholecystogram was negative.

His last admission occurred in August 1973, again because of right flank pain and right upper quadrant abdominal pain. Physical examination at this time revealed a 4 cm abdominal mass in the right upper quadrant. Laboratory studies again were normal. A lung scan showed multiple areas of diminished perfusion compatible with multiple pulmonary emboli. The bone scan was normal. An IVP again showed a large right kidney, but with a definite mass in the right lower pole. This mass was avascular on renal arteriogram. An inferior vena cavogram showed either tumour or clot in the right renal vein extending into the vena cava (Fig. 4).

At surgery, through a midline incision, the vena cava was isolated and clamped. While the nephrectomy was being performed, the patient sustained a cardio-pulmonary arrest. He was resuscitated and the nephrectomy was completed. He was moved to the recovery room, where he again sustained a cardio-pulmonary arrest. He died despite attempts to revive him. The renal pathology revealed carcinoma.

Post-mortem examination showed multiple old pulmonary infarcts and a large tumour embolus in the right pulmonary artery.

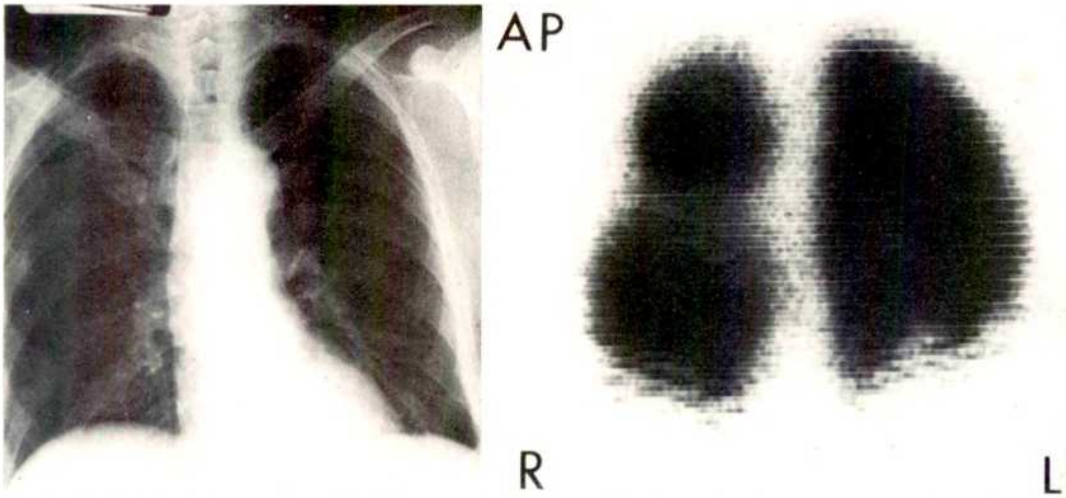

Fig. 5. Chest X-ray is unremarkable. Anterior lung scan shows a right-sided perfusion defect. This scan is labelled right and left.

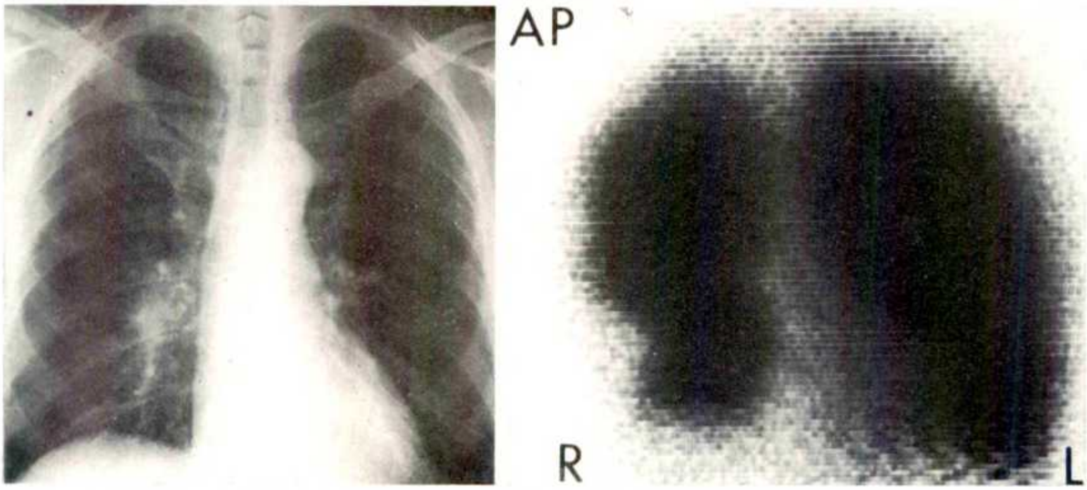

Fig. 6. Chest X-ray shows left costovertebral angle blunting. Anterior lung scan shows evidence of further emboli. It is labelled right and left.

Case 2. This 55-year-old white male was admitted in July 1974 with complaints of right chest pain and syncope that started while pushing a heavy object. Physical examination was unremarkable. Laboratory studies were normal. Chest X-ray was normal. A lung scan showed a right-sided perfusion defect and confirmed the clinical diagnosis of pulmonary embolus (Fig. 5). The patient was anticoagulated and discharged improved.

He was readmitted in August 1974 with evidence for further emboli on both chest X-ray and lung scan (Fig. 6). An inferior vena cava ligation was performed. The patient did well and was discharged.

1 month later he was readmitted complaining of afternoon fever and weakness. Physical examination was again unremarkable, but urinalysis showed haematuria and he was anaemic. An infusion IVP showed a mass in the lower pole of the right kidney. A right nephrectomy for renal carcinoma was done. The tumour involved the renal vein and pararenal tissue.

7 months later he died of metastatic renal carcinoma.

Comment

The presence of either inferior vena cava or renal vein involvement by tumour leads to an obvious chance of pulmonary emboli. Hyman and Leiter (1938) reported that 5·9% of renal carcinomas involve the vena cava; Arkless (1965) reported 9·2% and Svane (1969) reported 9·5%. Obviously, renal vein involvement must be higher, and indeed McDonald and Priestley (1943) noted 54%, Myers, Fehrenbaker and Kelalis (1968) noted 40%, and Marshall *et al.*, (1970) noted 33%.

Winterbauer, Elfenbein and Ball (1968) noted 31% of their patients with renal carcinoma had tumour emboli in the lungs. Arkless (1965) reported 26% of his patients having pulmonary lesions secondary to tumour emboli, despite the fact that Svane (1969) reported that tumour emboli usually do not lead to pulmonary metastasis. DeBoer and Prillevitz (1969) agree, stating that many tumour emboli degenerate, being destroyed or being incapable of growing to daughter tumours. Therefore, if 26 to 31% of patients had definite pulmonary metastasis, a much larger percentage of patients must have originally had pulmonary emboli. Furthermore, these figures do not account for the cases where fibrin clot adherent to tumour, rather than tumour, embolises.

Vigorous exercise and other physical activities in the presence of renal carcinoma may cause emboli.

Pulmonary embolism caused by carcinoma of the kidney may be more common than previously supposed. Patients with pulmonary emboli of obscure origin should therefore be investigated for renal carcinoma.

Summary

Two patients with renal carcinoma presenting with pulmonary emboli are discussed.

Pulmonary embolifrom renal carcinoma may be more common than previously supposed.

Evaluation for such tumours should be done in patients with pulmonary emboli of obscure origin.

LIBRARY MEDICINE

Francisco E. Jarmillo, MD, supplied 1 of the cases presented in this paper.

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The Authors

Richard L. Levine, MD, Assistant Professor.
Richard A. Airhart, MD, Instructor (Resident).

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Composition of Urinary Tract Calculi in Children of Different Ages

A. HODGKINSON
Medical Research Council, Mineral Metabolism Unit, The General Infirmary, Leeds

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Stones in children have become rare in Western countries since the disappearance of endemic bladder stones early in the present century and only a few studies of the composition of these stones have been made, mainly in the United States (Wenzl *et al.*, 1968; Paulson *et al.*, 1972; Bennett and Colodny, 1973; Malek and Kelalis, 1975) and in France (Brueziere, Gueriot and Lasfargues, 1974), Holland (Scholten, Bakker and Cornil, 1973) and Czechoslovakia (Vendl, 1975). These surveys show differences in stone-composition from one country to another, those from the United States and Czechoslovakia consisting predominantly of calcium salts, suggesting a metabolic cause, while those from France and Holland contained more magnesium ammonium phosphate, suggesting an infective origin. These differences appear to be age-related, infection stones being commonest in very young children and calcium stones most common in older children. Further evidence in support of this age-relationship has been obtained from observations on British children, on whom there has been little information hitherto.

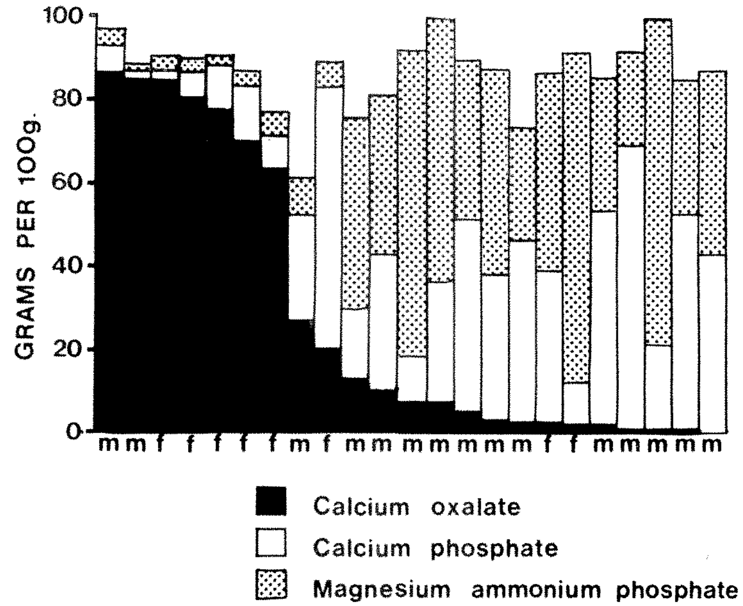

Fig. 1. Composition of calcium-containing stones from 23 children under 15 years of age. The letter at the foot of each column denotes the sex of the patient.

Materials

The survey covers the period 1966-76, during which time 32 calculi from children aged 15 years and under were received for analysis. These stones were removed from 25 patients (16 boys and 9 girls) and all were from the upper urinary tract except for 1 bladder and 1 urethral stone. The 25 patients represent 70% of all children treated for urinary tract calculi in the Leeds area (population 600,000) during the period 1966-76.

Methods

The stones were analysed by a quantitative chemical procedure (Hodgkinson, 1971) and were divided into three types: cystine, magnesium ammonium phosphate and calcium stones. Cystine stones were defined as those consisting predominantly of cystine, with or without other constituents, while magnesium ammonium phosphate stones were defined as stones containing more than 10% by weight of magnesium ammonium phosphate, usually in combination with calcium phospate. Calcium stones were defined as those composed predominantly of calcium oxalate or calcium phosphate and containing less than 10% by weight of magnesium ammonium phosphate.

Results

2 patients had cystine stones and the remainder had stones composed of calcium or magnesium salts. 6 patients produced more than 1 stone, but the stones formed by any 1 patient were generally similar in composition and the mean values were calculated in these cases. 15 patients (60%) had stones composed mainly of magnesium ammonium phosphate and calcium phosphate, 1 patient had a poorly mineralised stone consisting mainly of calcium oxalate and calcium phosphate, and the remainder (28%) had stones composed predominantly of calcium oxalate (Fig. 1).

Figure 2 shows the stones, classified on the basis of their main mineral components, in relation

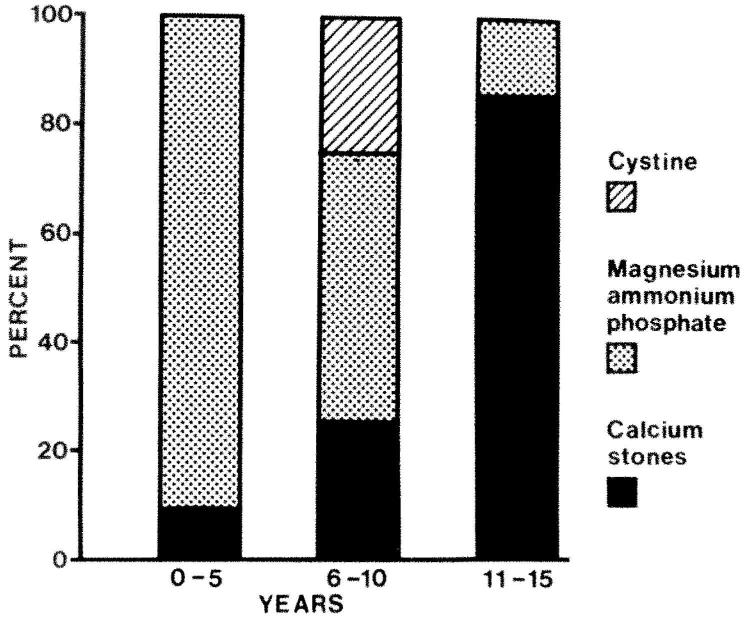

Fig. 2. Percentage occurrence of different types of stones in relation to age. The numbers of patients in the three age-groups were 11, 8 and 6 respectively.

to the ages of the patients. This shows that the youngest children had stones consisting predominantly of magnesium ammonium phosphate while the older children had stones composed principally of calcium salts.

Discussion

Most of the children in the youngest age-group had a *Bacillus proteus* infection, and 2 of these patients also had anatomical abnormalities in their urinary tracts (megaureter in each case). Only 1 child in this group had a calcium stone. This patient had a massive bowel resection for volvulus shortly after birth, with subsequent diarrhoea, and it is likely that this stone, which was composed mainly of calcium oxalate, was due to increased oxalate absorption and hyperoxaluria secondary to the bowel resection (Earnest *et al.*, 1974). By contrast, only 1 of the children in the 11-15 year old group had an infection stone; this patient had epispadias and a proteus infection.

The present survey provides further evidence of two types of paediatric stone disease: (1) infection stones, composed largely of magnesium ammonium phosphate and occurring mainly in children under 5 years of age, (2) stones composed mainly of calcium oxalate or calcium phosphate, occurring mainly in older children. The reason for the variation in the reported incidence of these 2 types of stone in different countries is still not entirely clear, but at least some of the variation is probably due to methods of selection.

Summary

The composition of urinary tract calculi in children in relation to their age has been examined and comparisons have been made with other published series.

It is concluded that paediatric stone disease can be divided into two main types: (1) infection stones, composed largely of magnesium ammonium phosphate and occurring mainly in children under 5 years of age, (2) calcium stones, occurring mainly in older children.

The author wishes to thank Mr P. B. Clark and Mr R. E. Williams, Department of Urology, Leeds General Infirmary, and Mr P. H. Smith, Department of Urology, St James's Hospital, Leeds, for permission to consult the hospital records of patients under their care.

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The Author

A. Hodgkinson, DSc, FRIC, Assistant Director.

Requests for reprints to Dr Hodgkinson at the M.R.C. Mineral Metabolism Unit, The General Infirmary, Leeds LS1 3EX

British Journal of Urology (1977), **49**, 456 ©

Short Case Report

An Unusual Penile Injury

Case Report

The exact circumstances surrounding the injury are not clear but apparently the patient, a 7-year-old boy, had disturbed a horse which had been grazing. The horse had lunged at him and bitten him between the legs. A full examination of the penis was only possible after the administration of a general anaesthetic. There was a ragged laceration of the foreskin and on retraction of it the glans distal to the corona was found to have been bitten off (Fig. 1). The foreskin was removed and the remnants of the glans was "tidied up". The urethra was spatulated and sewn to the glans with polyglycolic acid sutures. He was able to pass urine spontaneously the following morning and he was discharged home 5 days later. He has now (4 months later) developed meatal stenosis (Fig. 2).

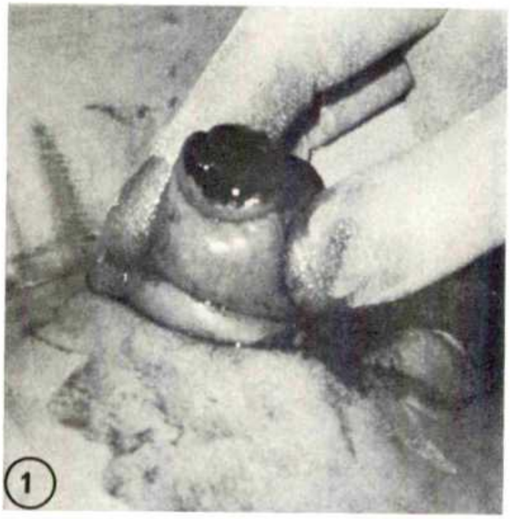

Fig. 1. The appearance of the glans of the penis after retraction of the foreskin.

Comment

Penile injuries in children are uncommon and usually consist of the foreskin being caught in a trouser zip. Other forms of injuries such as those caused by "falling" lavatory seats have also been reported (Editorial, 1973). Despite "spatulating" the urethra meatal stenosis has developed. This has been treated by a meatoplasty. As the corona was left intact the penis should function normally from the sexual point of view.

I would like to thank Mr G. S. Anderson for his permission to publish this case.

J. R. C. Logie
Royal Northern Infirmary, Inverness

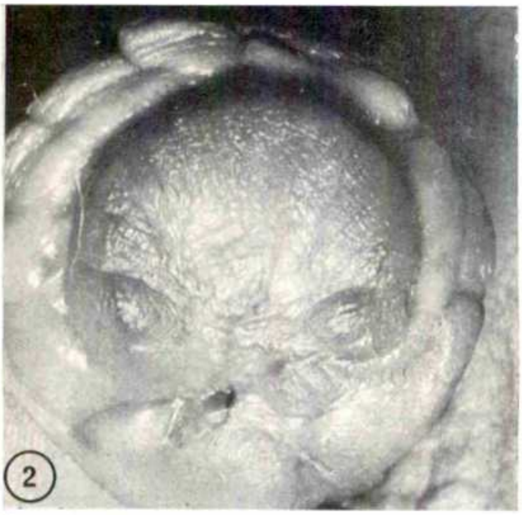

Fig. 2. 4 months later meatal stenosis has developed.

Reference

Editorial, 1973. *Journal of the American Medical Association*, Vol. 224, p. 1414.

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Clinical Evaluation of the Makari Test in Urological Malignancies

K. W. MUNSON and D. E. H. TEE
Departments of Urology and Immunology, King's College Hospital, Denmark Hill, London SE5 9RS

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In 1955, Makari reported the existence of carcinoma-specific antigens in the sera of subjects with carcinoma. Subsequently, he also detected tumour-specific antigens in subjects with malignant tumours (Makari, 1955, 1958) in response to which serum antibodies were produced. Both antigens and antibodies were demonstrated by using the Schultz–Dale technique. According to Makari, these antigens were polysaccharides or glycoproteins and this view was later supported by other workers (Smith, 1963; Jeanloz, 1970). These antigens are referred to as tumour polysaccharidal substances (TPS).

Since, for technical reasons, the Schultz–Dale test was not suitable for general diagnostic testing, Makari sought to develop a more practical procedure. The reaction of the skin to pneumococcal capsular polysaccharidal antigen and the apparent polysaccharidal nature of the TPS antigens prompted Makari to develop an intradermal skin test. Makari was able to show that TPS antigens derived from human carcinoma, sarcoma and lymphoma were capable of inducing immediate erythematous reactions when injected intradermally after complexing with either untreated or trypsinised serum from the patient being tested. A positive result consists of an erythematous reaction to any one of the antigens whose mean diameter compared to that given by a control injection, without antigen, is greater than 1·35. Makari reported that the tumour skin test gave positive results in most patients with early non-metastatic carcinoma and in a lower proportion of patients with metastases. Positive reactions were found in patients with neoplasia of a wide variety of organs and also in the presence of a group of diseases which included hepatic cirrhosis, ulcerative colitis, diverticulitis and peptic ulcer. The results of a completely independent study, in which possible investigator bias was eliminated by means of a double-blind controlled procedure, have previously been reported (Tee, 1973), which concluded that the test might have a useful place in the differential diagnosis and staging of tumours, in monitoring response to treatment and in the detection of tumour recurrence.

The test has recently been modified in order to increase the sensitivity and to decrease the positive reactions in patients with non-neoplastic diseases. A pilot study using this modification performed in November 1975 suggested that the test was able to detect over 80% of patients with urological malignancy (Tee, 1976). These improved results prompted a wider study of the test and its possible role in the management of urological malignancy. Recent studies in the USA are also showing improved results with the modified test (Makari and Goddard, 1976).

Materials and Methods

Antigens. Tumour polysaccharidal substances (TPS), prepared from mitochondrial fractions of cancerous tissues derived from lung carcinoma, sarcoma and lymphoma and subjected to vigorous physical and chemical treatment, were supplied by Ormont Diagnostics Limited.

Trypsin Solution. Lyophilised trypsin (Tryptar, Armour Pharmaceutical Co., Phoenix, USA) was dissolved in sterile isotonic saline solution to give the final concentration of 0·02 mg/ml.

Sera. Blood was obtained from a vein of the patient to be tested, allowed to clot and the serum separated. 0·4 ml serum was incubated in a NIB tube for 1 hour at 37°C. After absorption, the serum was diluted to 1 : 10 in sterile 0·9% sodium chloride solution. The test preparations were prepared aseptically; 0·1 ml of diluted serum was pipetted into each of 8 sterile tubes labelled 1 to 8. 0·1 ml of isotonic saline was added to each of tubes 1, 2, 3 and 4 and 0·1 ml of trypsin solution was added to each of tubes 5, 6, 7 and 8. The rack was shaken and left at 5°C for 30 minutes. Then 0·1 ml of sterile isotonic saline was added to tubes 1 and 5, and 0·1 ml of TPS-I to tubes 2 and 6, 0·1 ml of TPS-II to tubes 3 and 7 and 0·1 ml of TPS-III to tubes 4 and 8. The rack was shaken gently and placed in the refrigerator for a minimum of 30 minutes at 5°C. An 0·1 ml aliquot from each tube was injected intradermally using the patient's skin on either side of the spinal column starting about 8 cm below the prominence of the seventh cervical vertebrae. After an interval of 1¼ minutes from the first injection, the longest diameter of the erythema and the diameter at right angles to this were marked out and measured at each injection site sequentially. The study was carried out double-blind. The syringes were coded by an assistant according to a table of random numbers. Thus, the administrator neither knew the material injected into any particular site nor the patient's diagnosis. Subsequently, the mean diameter of erythema was obtained for each injection site after decoding. The ratios of the mean diameters of the antigen injections over that of the appropriate serum control were then computed. A ratio greater than 1·35 for any of the TPS injections constituted a positive result. This ratio was established by Makari (1969) following an investigation of the distribution of test ratios in groups of healthy volunteers and patients suffering from neoplastic and non-neoplastic disease.

Patients. Patients, admitted to hospital suspected of having a tumour, or who had had a previously treated tumour and were admitted for review, were asked to undergo the test and their consent obtained. Tests were performed preoperatively on in-patients, and occasionally on outpatients.

Disease Status. Diagnosis and staging of carcinoma was made by histological examination of tissue when available, and otherwise by clinical and operative assessment of the patient.

Cytology. Cytological examination of the urine was carried out, where relevant, as part of a correlating study.

Table I

Delayed Hypersensitivity Skin Testing
(0·1 ml intradermal injections—forearm. Rad—48 hours)

Antigen	Dilution	Criteria of positive reaction
Tuberculin	1 : 10,000	Induration, 1 cm or greater
Candida	1 : 1,000	
Trichophytin	1 : 20	
Streptokinase/Streptodornase (Varidase)	1 : 20	Induration, 2 cm or greater

Table II

Patients with Primary and Recurrent Malignancy

	Primary		Recurrent	
Makari test	Positive	Negative	Positive	Negative
All patients	35	15	60	50
Excluding known anergic patients	35 (95%)	2	60 (74%)	21

Detection of Anergy. When tumour was present, confirmed either histologically or clinically, in the presence of a negative Makari test, delayed hypersensitivity skin testing was performed. Patients were injected with 4 recall antigens, rather than 1, to increase the chance of detecting prior exposure and sensitisation. The patient was judged to be "anergic" when negative responses were obtained with all 4 antigens (Table I).

Results

The patients have been divided into those with (1) confirmed malignancy at the time of test, (2) previously treated carcinoma in whom there was no clinical or histological evidence of recurrence ("recurrence-free"), and (3) non-malignant disease.

The test was performed in 50 patients with untreated primary cancer and in 110 with treated cancer who had evidence of recurrent malignant disease. In patients with primary tumours, 35 had a positive test; in the remainder, 13 had delayed hypersensitivity skin tests and were shown

Table III

Distribution by Stage of Disease
of 160 Patients with Primary and Recurrent Malignancy

		Makari negative	
	Makari positive	"Anergic"	Not tested for anergy
Stage I (non-invasive)	71	12	4
Stage II	11	16	6
Stage III	4	7*	6
Stage IV	9	7*	7
Totals	95	42	23

* 9 died of tumour within 3 months of test.

Table IV

128 "Recurrence-free" Patients
(Previously treated with no evidence of clinical recurrence at time of initial test)

Initial test	Makari negative 80 (63%)		Makari positive 48 (37%)	
Follow-up	Remaining negative	Conversion to positive	Remaining positive	Conversion to negative
"Recurrence-free"	4	1	0	0
Malignancy or premalignancy	0	5*	13†	0
Non-malignant disease (co-existing)	0	0	5‡	0
No. followed-up	4	6	18	0
Awaiting follow-up	70		30	

* Proven recurrences, 4; positive cytology, 1.
† Proven recurrences, 2; Positive cytology, 8; Leukoplakia, 1; Bronchial carcinoma, 2.
‡ Diverticulitis, 4; Peptic ulcer, 1.

Table V

Patients with Non-malignant Disease

Total: 70	
Excluding 5 who developed suspect or proven cancer	65
Makari negative	40 (62%)
Makari positive	25 (38%)

Diagnosis	Positive	Negative
Benign prostatic hyperplasia	14	12
Haematuria	9 (3)*	10
Others	7 (2)*	18

* 5 patients subsequently placed in cancer category.

to be "anergic", while the immunological status was not determined in the other 2. Thus, excluding known anergic cases, the test identified malignant disease in 95% of this group. 14 of these patients were retested 7 to 10 days after surgical treatment of the primary. All of them converted from a positive Makari test preoperatively to a negative test after treatment, there being no evidence either histological or clinical of incomplete removal or of distant metastasis. 10 of these 14 patients have been followed up: 8 have remained negative and are disease free 4 to 8 months after initial treatment, whilst 2 have reconverted to a positive Makari at 5 and 6 months after treatment with evidence of recurrent tumour. Both these patients were treated for their recurrent disease, one converting to negative, the other awaiting a repeat test.

In the 110 patients with treated cancer who had evidence of recurrence, 60 had a positive test. Of the 50 with negative tests, 29 were tested for and shown to be anergic. 21 patients were not available to be tested. The test identified malignancy in 74% of these patients after exclusion of the known anergic cases. However, of those 21 patients whose immunological status had not been tested, a proportion almost certainly were anergic and the figure of 74% is therefore likely to be a low estimate. The distribution of patients with primary and recurrent tumours is shown in Table II. In all, there were 42 anergic patients, mostly with advanced malignant disease. This contrasts sharply with a high incidence of early malignant disease in patients with a positive Makari reaction (Table III), thus affirming the original claim that the test detects early as opposed to "late stage" disease.

In the 128 patients with previously treated carcinoma and no clinical evidence of recurrence, the test was negative in 80 and positive in 48 (Table IV). 10 of the 80 patients with an initial negative test, on follow-up, have shown that 4 remained negative and were "recurrence-free", while 6 converted to positive, of whom 4 had proven recurrence, 1 had positive cytology and 1 is unexplained to date.

Likewise, 18 of the 48 patients with an initial positive test have all remained positive: 13 had either suspected or confirmed malignancy, while 5 had non-malignant disease, as detailed in Table IV.

Data are not available on the remaining patients as they have yet to attend for their routine follow-up as directed by their clinician.

The control patients were admitted for a variety of benign urological conditions and the test was positive in 30. Subsequently, with further follow-up, 5 have been placed into a tumour category, thus reducing the number with positive reactions to 25 (Table V).

Statistical analysis, using chi square, of the incidence of positive results in patients with confirmed malignancy compared to those with non-malignant disease (after exclusion of anergic patients) shows a highly significant difference ($P > 0{\cdot}0001$).

Significance

We consider that the initial results given by this modified test could assist in the diagnosis of both primary and recurrent carcinoma, especially when anergic patients can be identified and excluded. We have shown, albeit in a small number, that with adequate excision of the tumour the test converts from positive to negative; should the test not convert, this may indicate inadequate primary treatment and that further or additional treatment is necessary. A much longer follow-up is necessary to determine how much help the test will be in monitoring the progress of the patient and in detecting early recurrence when further treatment may be instituted.

It is a disadvantage that the test is positive in a number of patients with non-malignant disease, nevertheless, a positive Makari test in such patients does not exclude the coexistence of neoplastic disease.

With regard to the safety of the test, we wish to point out that in neither the present nor previous studies have signs of toxicity or carcinogenicity been observed. Animal tests (Perkins, 1971; Wells Laboratories, Inc., 1972) have also failed to demonstrate any toxic or carcinogenic effects. In the present study, considerable care was taken to exclude bias. The precautions included measures to ensure that the physician administering the test was unaware of (*a*) the nature of the injections at any particular site, (*b*) the patient's diagnosis, (*c*) the investigations performed. The diagnosis was finally established in the majority of patients after exploratory surgical procedures had been performed and the resulting histological specimens examined. It is therefore reasonable to believe that these results were not influenced by observer bias and that they derive from valid biological activity of the test.

Summary

The results of a double-blind controlled study of the modified Makari skin test for the detection of cancer are described.

The test identified malignant disease in 95% of 37 patients with primary cancer and in 74% of 81 with recurrent cancer after the exclusion of "anergic" patients.

The study suggests that the test will be useful in the monitoring of primary treatment and in the detection of recurrent malignancy.

We should like to thank our colleagues for allowing us to study their patients and Miss Caroline Barrett for technical assistance. One of us (K. W. M.) gratefully acknowledges the support of Mr J. P. Williams, Greenwich District Hospital.

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The Authors

K. W. Munson, FRCS, Senior Urological Registrar, King's College Hospital. (Honorary Senior Registrar, The Institute of Urology.)

D. E. H. Tee, FRCPath, Consultant Immunologist, King's College Hospital.

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Short Case Report

Persistent Priapism in Rabies

Case Report

A 25-year-old man reported with priapism of 1½ days duration. He had a history of sexual exposure followed by urethritis 6 days prior to this, which had been treated by his local doctor.

On examination the priapism was confirmed and as the blood count and smear proved negative for leukaemia, general anaesthesia with relaxant was tried. The priapism subsided completely under anaesthesia but as the patient came out of it, he developed classical signs of hydrophobia. On enquiry, the relatives remembered the dog-bite this patient had received 4 months previously on his right thigh. The dog died 3 days later and was proved rabid. However, the patient took only village cure and forgot the whole thing.

This patient was transferred to a rabies centre where he died of established rabies.

Comment

Priapism as the only early symptom of rabies is quite rare. This could have been caused by local irritation due to the nearness of the dog-bite.

P. M. S. TALAULICAR
SMT. Laxmibai Talaulicar Memorial Hospital, Panaji
Goa, India

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Perianeurysmal Retroperitoneal Fibrosis: Two Cases Responding to Steroids

CHARLES A. C. CLYNE and G. F. ABERCROMBIE

Department of Urology, St Mary's Hospital, Portsmouth; Department of Vascular Surgery, Hammersmith Hospital, London

(Received 2 May, 1977; accepted for publication 22 July, 1977)

Retroperitoneal fibrosis due to aortic aneurysm is a rare cause of ureteric obstruction.

We present 2 cases successfully treated with corticosteroids.

We are unaware of any previous reports of ureteric obstruction due to perianeurysmal fibrosis responding to steroids.

Case Reports

Case 1. A 51-year-old male presented in February 1976 with a history of right loin pain. He had passed a ureteric stone in 1963, had a hernia repair in 1974 and a myocardial infarct later that year. Examination of the abdomen revealed a prominent aorta as the only abnormal finding. All ordinary investigations were normal and an IVP carried out was also considered normal (Fig. 1).

5 months later, due to continuing symptoms, another IVP revealed a non-functioning left kidney (Fig. 2) and he was referred to St Mary's Hospital, Portsmouth, for a urological opinion. His Hb was 12·7 gm %, ESR 70 mm/hour,

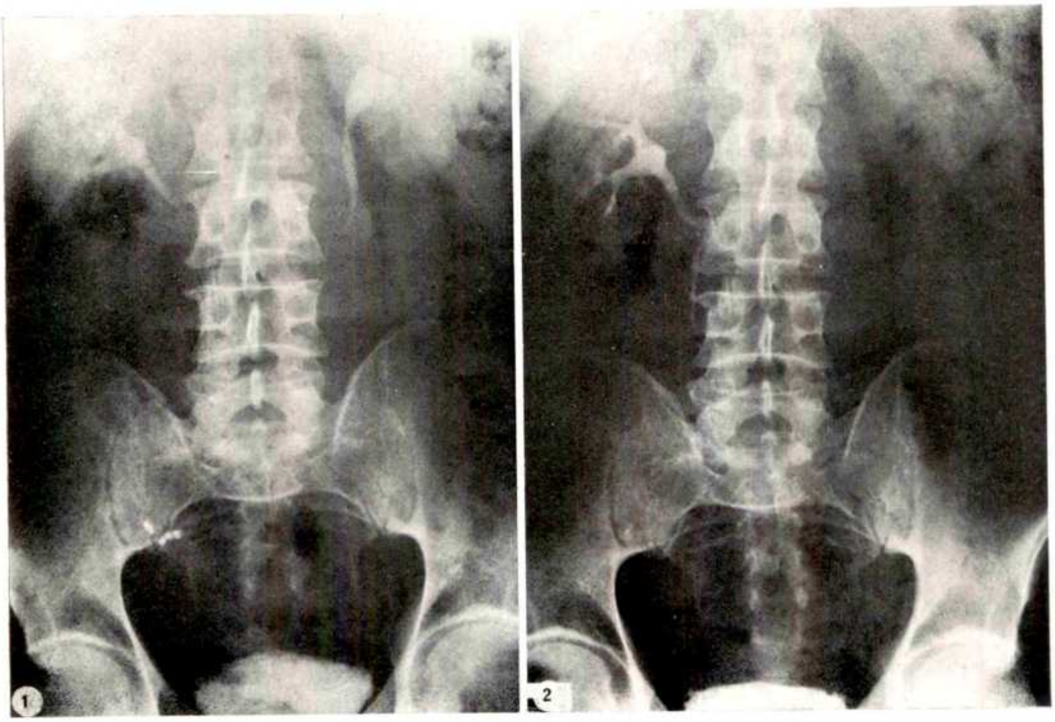


Fig. 1. Case 1: Pyelogram on first presenting in February 1976.

Fig. 2. Case 1: Pyelogram 5 months later on referral with non-function of left kidney.

urea 7·6 mmol/l, and creatinine 0·16 mmol/l. Autoimmune profile showed no abnormalities and his MSSU was sterile.

Cytoscopy, examination under anaesthetic and bilateral ureterography were carried out and revealed an abdominal aortic aneurysm, normal appearance of the bladder and bilateral ureteric obstruction (Fig. 3). A clinical diagnosis of ureteric obstruction due to perianeurysmal fibrosis was made.

In view of his previous myocardial infarct and the small size of the aneurysm, non-operative management was instituted and Prednisolone 5 mg t.d.s. was given. IVP 6 weeks later showed that function had returned to the left kidney (Fig. 4). Serum creatinine had fallen to 0·11 mmol/l. He was well when last seen at 8 months follow-up, and his ESR had fallen to 10 mm/hour.

Case 2. A 64-year-old male presented to another hospital with a 2-year history of upper abdominal pain, low backache and 3-stone weight loss. Investigations had proved normal and a laparotomy had been carried out with a provisional diagnosis of pancreatic carcinoma. However, at laparotomy, an aortic aneurysm was found and the patient was referred to the Vascular Surgery Department of the Hammersmith Hospital.

On the afternoon of admission the patient became hypotensive with severe left-sided abdominal pain and a diagnosis of leaking aortic aneurysm was made.

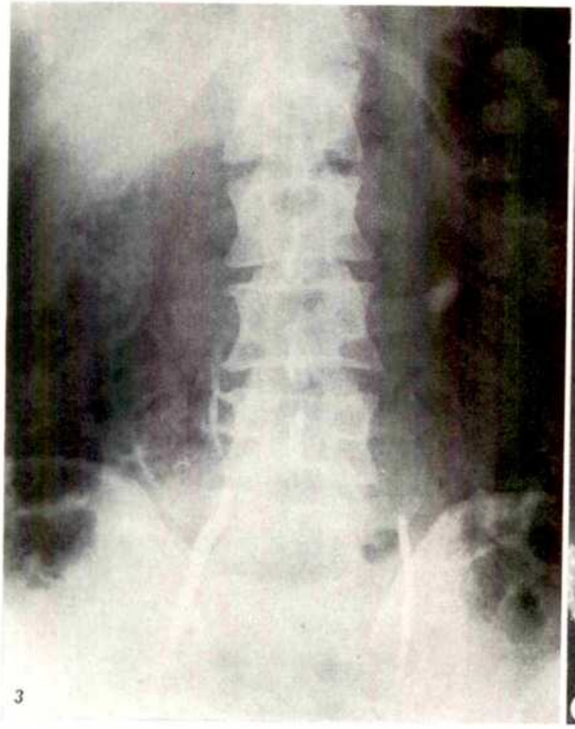
His Hb was 11·2 gm % and blood urea 12·6 mmol/l. Laparotomy carried out showed dense fibrosis involving the whole posterior abdominal wall. The aneurysm was unresectable due to the density of the fibrosis and the ureters could not be located. The right kidney was found to be enlarged. The abdomen was closed after taking a biopsy which showed the typical appearance of retroperitoneal fibrosis.

On the twelfth postoperative day an IVP showed dilated calyces, particularly on the right with obstruction of both ureters. In view of the findings Prednisolone 5 mg q.d.s. was commenced.

2 months later, IVP showed dilatation of the upper calyces on the right only, with no sign of obstruction of the ureters.

4 months after presentation the blood urea was 8·3 mmol/l, and the patient was pain-free.

1 year after presentation, barium meal and gastroscopy were carried for upper abdominal pain. Atrophic gastritis was diagnosed and the steroids which had been stopped pending a diagnosis, were restarted at a dose of 5 mg b.d.



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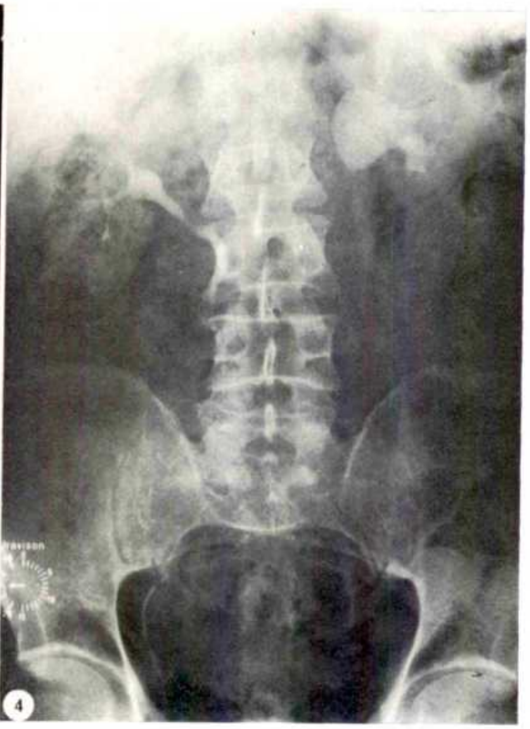

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Fig. 3. Case 1: Bilateral ureterograms showing bilaterally obstructed ureters.

Fig. 4. Case 1: Pyelogram after 6 weeks' treatment with steroids.

Table

No.	Author and year	Age and sex	Obstruction	Treatment		Outcome	Follow-up
				of aneurysm	of ureters, etc.		
1.	Schloss and Kaplan (1953)	67 M	Bilateral	Wiring	Ureteric catheters	Recovered	2 years
2.	De Weerd *et al.* (1955)	45 M	Bilateral with anuria	None	Ureterolysis and bilateral nephrostomies	Recovered	15 months
3.	Shumacker and Garrett (1955)	60 M	Bilateral with anuria	Resected	Ureterolysis	Recovered	5 months
4.	Crane (1958)	60 M	Unilateral	None	Ureterolysis	Died of ruptured aneurysm	2 months
5.	Crane (1958)	53 M	Bilateral	Resected	Ureterolysis	Recovered	11 months
6.	Pearlman and Mackey (1960)	62 M	Bilateral with anuria	Resected	Left nephrostomy	Died	26 days
7.	Albers and Bettaglio (1961)	50 M	Unilateral	Resected	Ureterolysis	Recovered	2 months
8.	Cottler and Immergut (1961)	54 M	Unilateral (solitary kidney)	None	Ureterolysis nephrostomy	Died of ruptured aneurysm	2 years, 3 months
9.	Spittel and Hunt (1966)		Bilateral	Resected	Ureterolysis		
10.	Labardini and Ratliff (1967)	60 M	Bilateral	Resected	Ureterolysis	Recovered	None given
11.	Abercrombie and Hendry (1971)	65 M	Unilateral (solitary kidney)	None	Ureterolysis	Recovered	12 months
12.	Wagenknecht and Madsen (1970)	74 M	Bilateral	Resection abandoned	None	Recovered	5 months
13.	Wagenknecht and Madsen (1970)	65 M	Bilateral	None	Ureterolysis	Recovered	4 months
14.	Kitchen and Morris (1972)	69 M	Bilateral	Resected	None	Recovered	3 months
15.	Friedel *et al.* (1973)	67 M	Bilateral with anuria	Resection abandoned	Bilateral nephrostomies	Recovered	12 months
16.	Rothman and Kendall (1974)	57 M	Bilateral	Resected	Ureterolysis	Recovered	3 months
17.	Boontje *et al.* (1974)	57 M	Unilateral	Resected	Ureterolysis	Recovered	12 months
18.	Bouffioux (1975a)	66 M	Unilateral	None	None	Died of ruptured aneurysm	None
19.	Bouffioux (1975a)	58 M	Bilateral	None	Ureterolysis	Died of infarct	6 months
20.	Bouffioux (1975a)	59 M	Bilateral	Resected	Ureteric catheters Bilateral nephrostomies	Recovered	3 years
21.	Bouffioux (1975b)	60 M	Bilateral	Resection abandoned	Temporary bilateral nephrostomies	Recovered	3 years
22.	Present case (1977)	51 M	Bilateral	None	Steroids	Recovered	6 months
23.	Present case (1977)	64 M	Bilateral	Resection abandoned	Steroids	Recovered	2 years, 6 months

Prior to recommencing the steroids, the ESR was 59 mm/hour, but after 4 week's treatment this had fallen to 15 mm/hour.

When seen at 2½ year follow-up he was symptom-free and his blood urea was 6 mmol/l.

Discussion

Since one of us reviewed ureteric obstruction due to perianeurysmal retroperitoneal fibrosis (Abercrombie and Hendry, 1971), 12 further cases have been added to the literature (see Table). 3 cases described before 1950 remained essentially untreated and are not included here (Duchanoff, 1934; James, 1935; Goodwin and Shumacker, 1947).

In the fit patient ureterolysis and resection of the aneurysm must remain the treatment of choice. Temporary nephrostomies may be advisable. However, analysis of the 21 cases in the Table shows that surgery was directed at the kidneys and ureters in 18 cases (86%), and at the aneurysm in 14 cases (67%). However, in 3 cases (and 1 of ours) resection had to be abandoned. Hence successful surgery on the aneurysm was only possible in 11 cases (52%).

Surgery provides immediate relief of urinary obstruction and removes the predictable mortality of ruptured aneurysm (Colt, 1927), although some authors suggest a different aetiology for "inflammatory" aneurysms and hence a different prognosis (Walker *et al.*, 1972).

In unfit patients, those refusing surgery and those without bilateral complete ureteric obstruction, it is possible to resolve the obstructive nature of the fibrosis by steroids. The use of corticosteroids for idiopathic retroperitoneal fibrosis was first recorded in 1958 (Cosbie Ross and Tinckler, 1958), being most successful in early cases (Ochsner *et al.*, 1975), but we know of no other cases of ureteric obstruction in perianeurysmal retroperitoneal fibrosis that have responded to steroids.

Although the causative factors in retroperitoneal fibrosis may vary (*i.e.* methysergide, disseminated malignancy, aneurysms) or may not be identified as in idiopathic cases, it is reasonable to suppose that the process is similar in all cases and therefore that steroids should be no less effective in the perianeurysmal cases.

Summary

We have presented 2 cases of perianeurysmal retroperitoneal fibrosis causing ureteric obstruction that resolved with steroids. 21 cases treated surgically are analysed.

I would like to thank Mr C. W. Jamieson and Mr J. Castro for allowing me to report their case.

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The Authors

C. A. C. Clyne, FRCS, FRCS(Ed) Registrar in Vascular Surgery, Hammersmith Hospital, London.
G. F. Abercrombie, FRCS, Consultant Urological Surgeon, St Mary's Hospital, Portsmouth.

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Short Case Report

Porphyria Cutanea Tarda induced by Oestrogen Therapy

Table

			Date		
	Investigation	26.12.75	11.2.76	10.8.76	Normal values
Urinary	Coproporphyrin	1105 nmol/l	128	60	1-432 nmol/24 hr
Urinary	Uroporphyrin	2004	188	Nil	0-49 nmol/24 hr
Urinary	γ Aminolaevulinic acid	$5{\cdot}9 \times 10^3$	$2{\cdot}1 \times 10^3$	11	0-40 nmol/24 hr
Urinary	Porphobilinogen	$6{\cdot}6 \times 10^3$	24×10^3	1·6	0-6 nmol/24 hr
Faecal	Coproporphyrin		40		0-76 nmol/g dry wt
Faecal	Protoporphyrin		13		0-200 nmol/g dry wt

Case Report

In November 1975 a 77-year-old man presented with a 3-month history of blistering on his neck and hands associated with increased fragility of his skin.

In 1961 a clinical diagnosis of carcinoma of prostate had been made and therapy with stilboestrol 30 mg/day commenced. The dose was reduced to 15 mg/day in 1962 and to 5 mg/day in 1971. In 1973 his therapy was ethinyl oestradiol 2 mg/day and from October 1975 0·02 mg/day.

Investigations in November 1975 revealed a normal blood count but slight derangement in his liver enzyme and serum iron indices. The characteristic biochemical abnormalities of porphyria cutanea tarda were noted (Table).

Comment

Oestrogen-induced porphyria cutanea tarda has been reported in patients with carcinoma of prostate. The diagnosis is suggested by blistering of the skin in a light-sensitive distribution. Other features are increased skin fragility, hyperpigmentation and hypertrichosis. The biochemical abnormalities are an increase in urinary uroporphyrin and coproporphyrin excretion. Haemosiderosis is frequently associated and may be related to the high alcohol intake of many of these patients.

In 21 men described by Roenigk and Gottlob (1970) the condition developed from 1 month to 8 years after the initiation of therapy. Diethyl stilboestrol, from 5 mg to 60 mg daily, was the most commonly prescribed drug. Ethinyl oestradiol and stilboestrol diphosphate had been prescribed for the patient reported by Klaber, Baker and Warin (1976).

In this case it was possible to stop the administration of oestrogens. No therapeutic measures such as phlebotomy were employed and spontaneous improvement occurred over 6 months.

MARION I. WHITE
Aberdeen Royal Infirmary, Aberdeen AB9 2ZB

Reprints: Dr M. I. White, Registrar, Department of Dermatology, University of Aberdeen, University Medical Buildings, Foresterhill, Aberdeen AB9 2ZD.

I am grateful to Mr William H. H. Garvie, Consultant Surgeon and Dr Robert A. Main, Consultant Dermatologist, for permission to publish this case history.

I thank the Department of Materia Medica, Stobhill Hospital, Glasgow, for the porphyrin estimations.

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Primary Obstructed Megaureter

P. PAGANO and G. PASSERINI
Department of Paediatric Urology, University of Padua

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Megaureter is one of the most controversial topics in urology. Many theories have been offered as to the aetiology and several classifications have been devised (Johnston, 1967; Hendren, 1969; Mark and Noel, 1969; Tanagho, Smith and Guthrie, 1970; McLaughlin, Leadbetter and Pfister, 1971; McLaughin et al, 1973; Belman, 1974; Whitaker, 1973; 1975; Abatangelo *et al.*, in press). Whitaker and Johnston (1975), including all forms of what they called "wide" ureters, classified them on the bases of stasis, obstruction and reflux. In our opinion the terminology applied to megaureter is too extensive and attempts to include the aetiological basis in classifications have

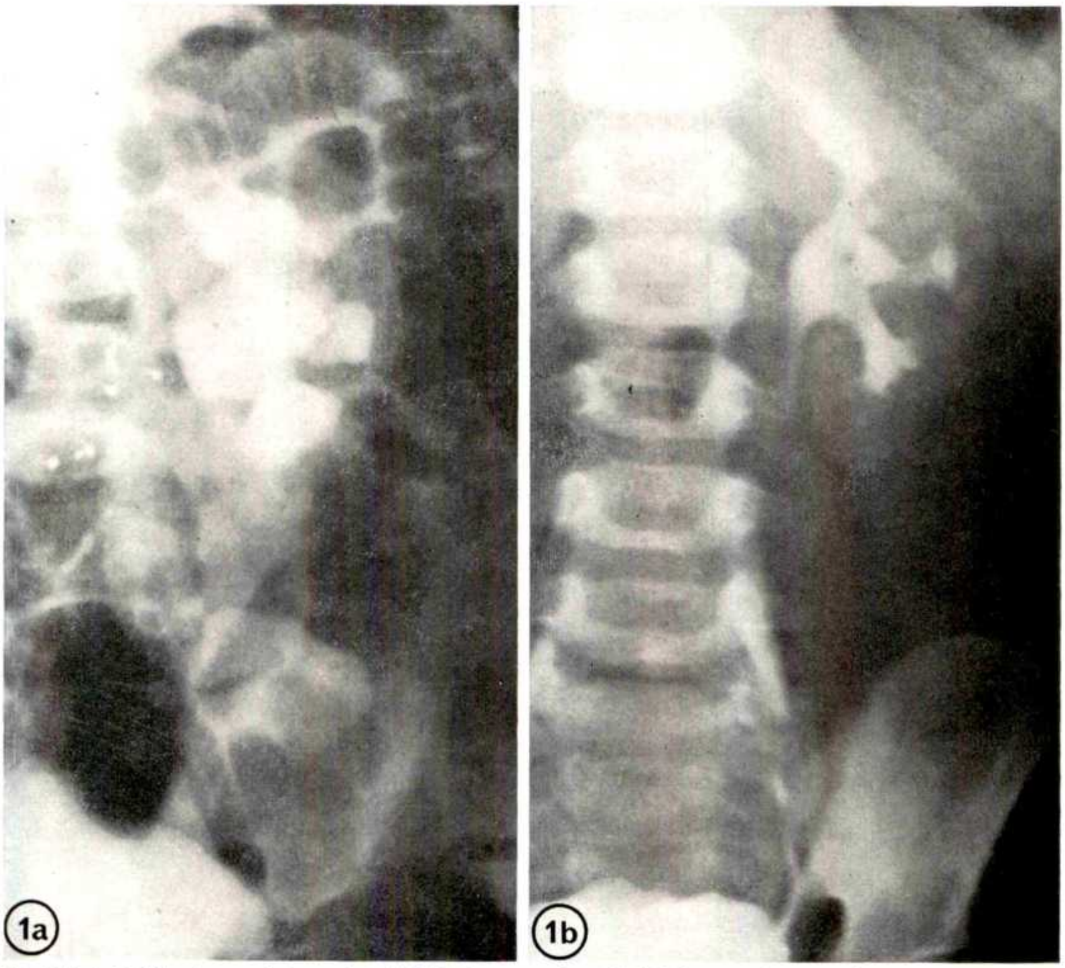


Fig. 1. Left POM in boy aged 1 month. (a) IVP before operation. (b) IVP 2 years after operation.

failed to clarify the situation. We believe it is important to make a clear distinction between the primary obstructed megaureter (POM) and other forms of wide ureter and we suggest the following divisions.

1. Primary obstructed megaureter (Williams and Hulme-Moir, 1970). Here the pathology is in the terminal part of the ureter and cystography is normal, without ureteric reflux.
2. Secondary megaureter which may be associated with (*a*) massive vesico-ureteric reflux, either primary or secondary, or with (*b*) bladder outflow obstruction.

The present article records our clinical experience with POM and evaluates the behaviour of these ureters in childhood and in adult life in the light of recent researches into their histochemical structure (Pagano *et al.*, 1976; Abatangelo *et al.*, in press).

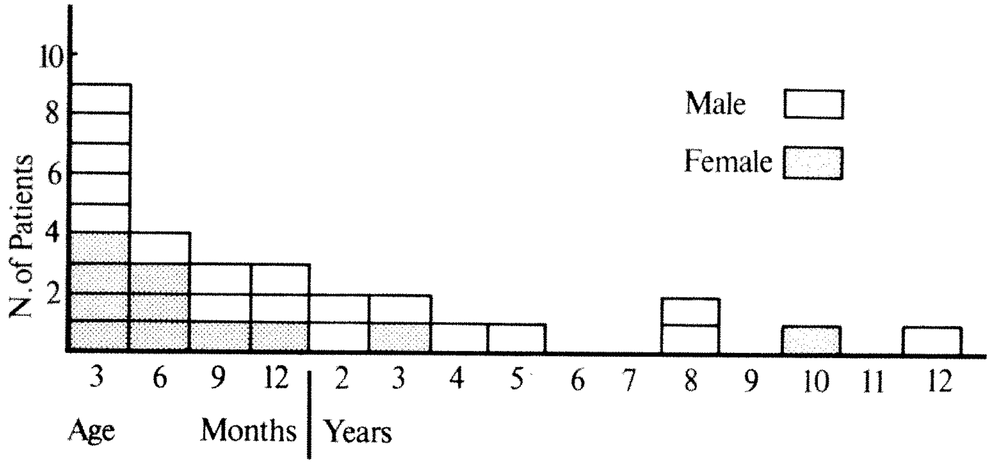
Table I

Primary Megaureter in Children
29 Pts 35 U.U.

Side of Megaureter	Male	Female
Left	11 (11)	3 (3)
Right	5 (5)	5 (6)*
Bilateral	2 (4)	3 (6)
Total	18 Pts (20 U.U.)	11 Pts (15 U.U.)

Chief Symptoms	
1—Infectiin	26
2—Pain	4
3—Anuria	1

* One patient with complete ureteric duplication.



Distribution of 29 Children with primary megaureter

Patients

Our series of POM comprises 46 patients with 57 affected ureteric units. There were 29 children, 18 boys and 11 girls, ranging in age from 1 month (Fig. 1) to 12 years (Table I), and 17 adults, 10 male and 7 female (Table II). The megaureter was bilateral in 5 children and in 4 adults. The contralateral kidney was congenitally absent in 3 patients; in 2 others it showed complete ureteric duplication. All patients were studied by urine culture, blood chemistry, glomerular filtration rate, excretory urography, micturating cystography and cystoscopy. Assessment of ureteric peristalsis was not found to be of prognostic importance since the absence of peristalsis may be merely a transient occurrence resulting from an episode of acute infection or a sudden increase in the degree of obstruction.

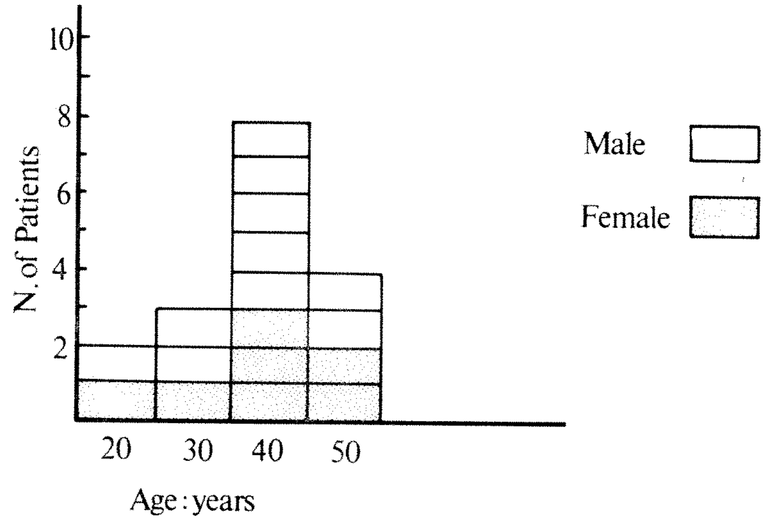
Table II

Primary Megaureter in Adults
17 Pts 22 U.U.

	Side of Megaureter	
	Male	Female
Left	4 (4)	2 (2)
Right	4 (4)	3 (4)*
Bilateral	2 (4)	2 (4)
Total	10 (Pts 12 U.U.)	7 Pts (10 U.U.)

Chief Symptoms	
1—Pain	14
2—Infection	11
3—Haematuria	5

* One patient with complete ureteric duplication.



Distribution of 17 adults with primary megaureter

Management and Results

Operation was performed on 51 megaureters; 6 megaureters in adults were treated without surgery. In our early operative cases we carried out ureteric reimplantation to the bladder by the Lich-Gregoir technique in 2 patients and by the Politano-Leadbetter method in 3. With later cases, narrowing of the ureter prior to reimplantation was performed. Since it is known that the operative results are less satisfactory in adults than in children, possibly because of the different structure of the ureteric wall (see below), we have performed a less extensive ureteric narrowing in the older patients. Temporary nephrostomy prior to ureteric surgery was necessary in 2 patients, a 3-year-old girl with a solitary kidney who became anuric and a 38-year-old man with bilateral megaureters (Fig. 2).

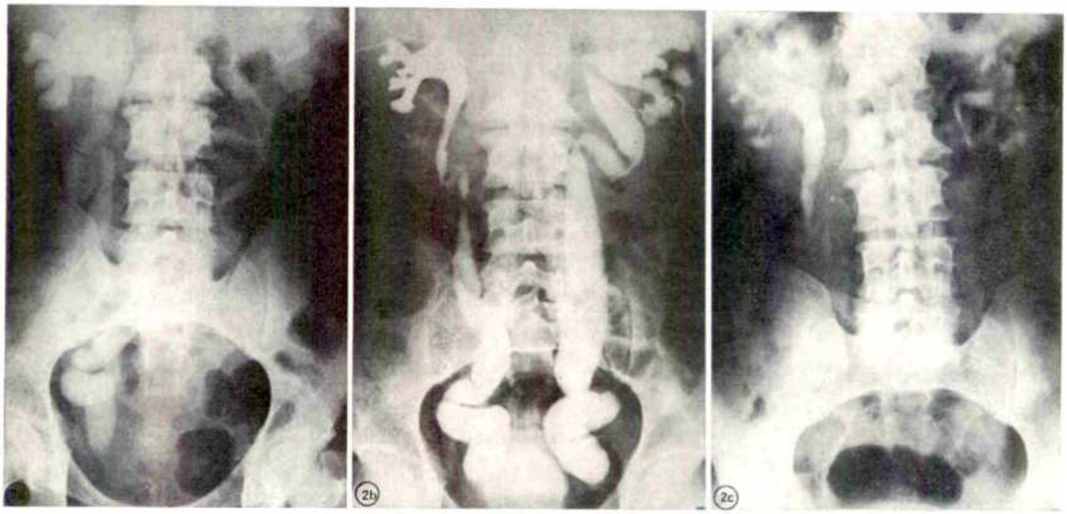


Fig. 2. Bilateral POM in 38-year-old man. (a) IVP showing right hydroureteronephrosis and severe functional impairment of the left kidney. (b) Bilateral nephrostograms 1 month after percutaneous nephrostomies. (c) IVP 2 years after bilateral ureteric reimplantation.

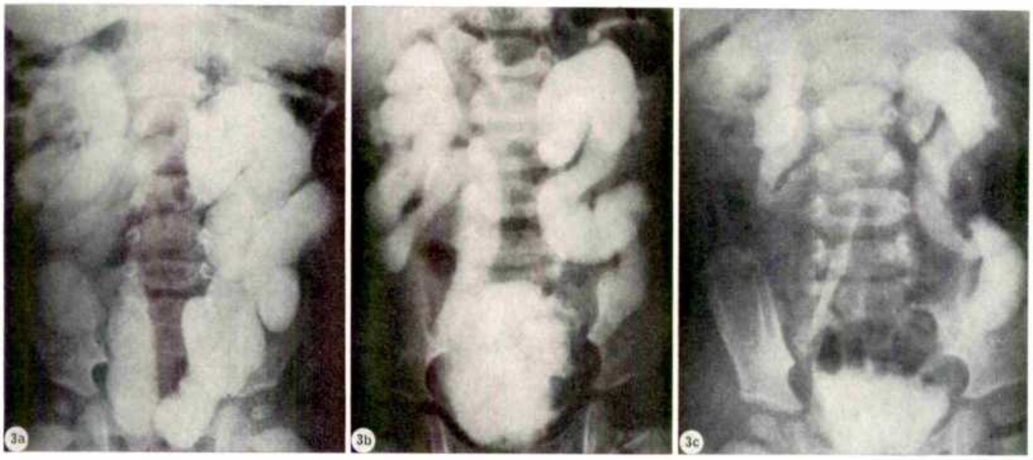


Fig. 3. 14-month-old boy with bilateral POM causing massive hydroureteronephrosis. (a) IVP before operation. (b) IVP 3 months after operation. (c) IVP 6 months after operation.

46 patients with 57 megaureters have been followed up for a minimum of 6 months; the average period was 3 years. 3 of 5 ureters reimplanted without operative narrowing subsequently showed vesico-ureteric reflux; 2 later underwent re-operation successfully. 3 postoperative urinary leaks occurred in patients who had had ureteric narrowing; in each a nephrostomy was performed promptly. In the 2 children affected the leak closed spontaneously; in the adult the fistula persisted and was followed by stenosis of the ureter. A 14-year-old boy had several episodes of urinary infection soon after operation and an excretory urogram showed increased ureteric dilatation; however, 3 months later the urogram demonstrated a dramatic improvement.

Renal function was initially severely impaired in a 3-month-old girl with a solitary kidney and in a 14-month-old boy with bilateral megaureters (Fig. 3). In both the glomerular filtration rate improved rapidly after operation and was normal within 6 months. In a 7-year-old boy with a solitary kidney (Fig. 4) the blood urea nitrogen was 3·2 mmol/l and the creatinine clearance 65 ml/min/1·73 m^2 on referral. After a successful operation, with radiological improvement, the glomerular filtration rate was unchanged during the first few months and then slowly deteriorated. Now, 6 years after surgery, the blood urea nitrogen is 3·5 mmol/l and the creatinine clearance 60 ml/min/1·73 m^2. Good results were obtained with the remaining megaureters with the exception of 5, 2 in children and 3 in adults, which showed no radiological improvement.

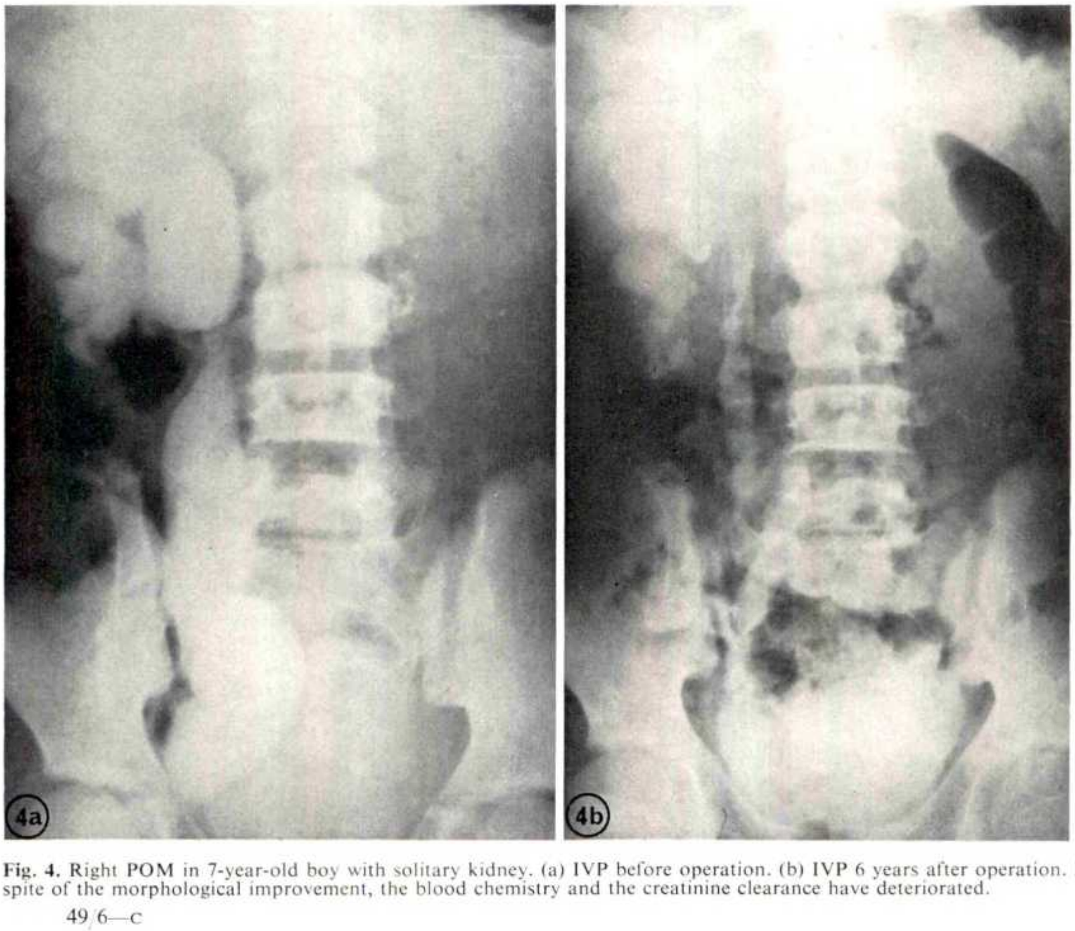


Fig. 4. Right POM in 7-year-old boy with solitary kidney. (a) IVP before operation. (b) IVP 6 years after operation. In spite of the morphological improvement, the blood chemistry and the creatinine clearance have deteriorated.

Pathology

Histological examination of the portion of ureter removed at operation was performed, particular attention being directed to the elastic component of the ureteric wall as compared with that of a normal ureter. The elastic tissue content was also evaluated by chemical and histochemical methods. As previously described (Pagano *et al.*, 1976; Abatangelo *et al.*, in press), these studies showed that the megaureters differed structurally in children and in adults and that both differed from the normal. In children, megaureters contain a marked increase in elastic tissue; in adults there is an increase in the amount of muscular tissue and a decrease in elastic content as compared with the normal ureter. In all affected ureters the terminal segment was narrow; its length varied from 0·5 to 4 cm.

Discussion

In our opinion, operation is always needed for POM in children. We carried out conservative management initially in 4 cases but recurrent episodes of infection later necessitated surgery. In infants, if renal function is impaired, prompt intervention is essential. From our experience, which is supported by reports in the literature (McCrory *et al.*, 1971; Mayor and Genton, 1974; Rizzoni *et al.*, 1975), when the glomerular filtration rate is less than 50% of normal, and surgery is performed after the age of 24 months, restoration of normal kidney function is not to be expected.

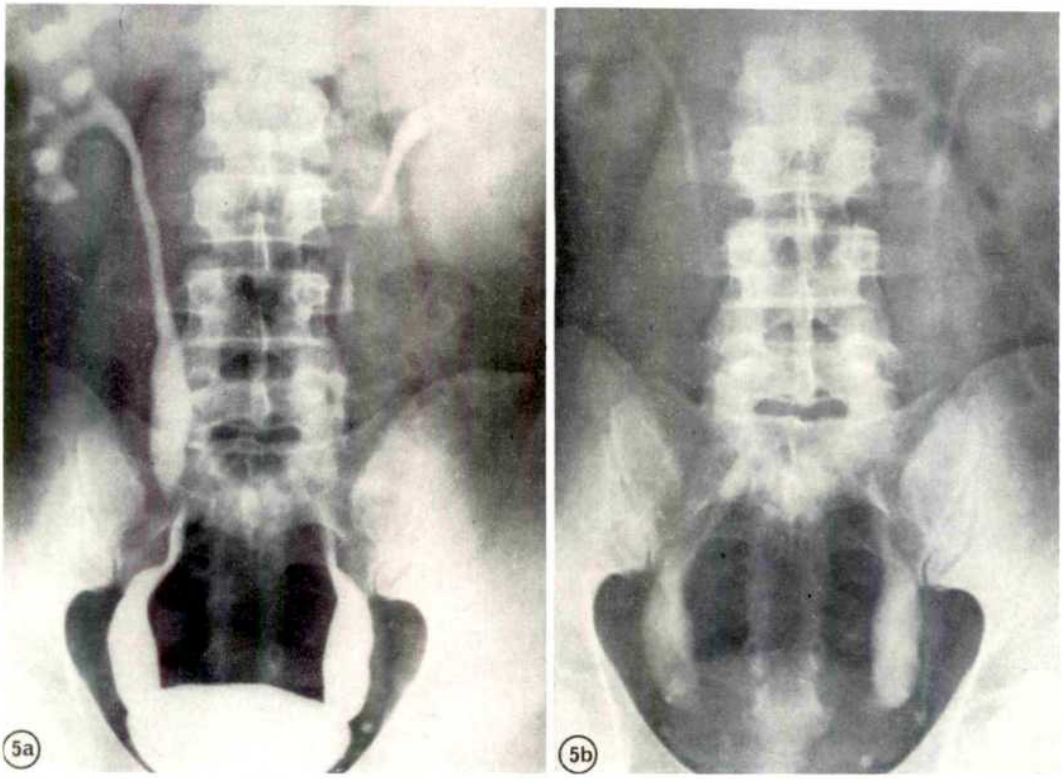


Fig. 5. Bilateral segmental POM in 42-year-old man. (a) IVP at age of 32 years. (b) IVP 10 years later showing no significant change.

Although precise predictions with POM are difficult, the disease tends to be more stable in adults than in children. In adults, therefore, when the ureteric dilatation is segmental only or when the ureter, although dilated along its entire length, is only mildly affected, we prefer non-operative management with regular review. 5 adults in our series have now been observed for periods of between 3 and 10 years. 4 remain asymptomatic; 1 has had 2 episodes of haematuria in 5 years. 1 adult has bilateral megaureters which have remained unchanged for 10 years (Fig. 5).

Summary

The clinical presentation and management of 57 primary obstructed megaureters in 46 patients, 35 of whom were children, are reported.

Indications for operation include pain, infection, progressive pyelo-ureteric dilatation and reduction in the glomerular filtration rate.

We have found that affected children cannot be managed successfully without operation.

Conservative treatment may be employed effectively in adults in whom the condition is often stable and complications are less frequent.

The preferred surgical technique is ureteric narrowing with reimplantation to the bladder by the Politano-Leadbetter method.

The results of surgery are less satisfactory in adults than in children. This may be related to the reduced quantity of elastic tissue in the ureteric wall in adult cases.

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The Authors

F. Pagano. M.D., Professor, Head of Department
G. Passerini. M.D., Assistant Professor

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Short Case Report

Death following Intravesical Formalin Instillation

Case Description

A 45-year-old woman with severe rheumatoid arthritis was admitted with a 2-year history of progressively worsening painful haematuria with clots. Her medication included cyclophosphamide 60 mg daily, as well as Depot Synacthen, Naprosyn, Indocid and paracetamol. Her admission haemoglobin was 6·4 g/100 ml. She was transfused, and treated to no effect with oral epsi-amino-caproic acid, continuous bladder irrigation and intravesical hydrocortisone. 50 ml of 10% formalin was then instilled into the bladder for 3 min under anaesthesia. The haematuria initially cleared, but recurred after 48 hours, necessitating a further instillation of 100 ml of 10% formalin for 5 min. She developed a coliform septicaemia and, 10 hours after the second procedure, developed severe dyspnoea followed by a fatal cardiac arrest. A blood sample taken shortly before death contained 40 mg formalin/100 ml. At post-mortem the bladder contained 1 litre of clot; there was no evidence of pulmonary embolism nor significant coronary arterial narrowing, though the lungs were firm and oedematous.

Comment

Introduced by Brown (1969), intravesical formalin instillation has become established as a treatment for refractory bladder haemorrhage, usually associated with tumour or cyclophosphamide therapy. There is no previous report in the literature of death following this procedure. Post-mortem examination of the bladder in patients with cyclophosphamide cystitis shows ulceration and denudation of the mucosa (Kalish *et al.*, 1973), changes which could allow the penetration of formalin into the blood-stream, possibly with toxic effects on lung tissue or the myocardium. In a patient already debilitated by blood loss and septicaemia such effects might be sufficient to lead to cardiac arrest.

Our thanks are due to Dr H. W. H. Kennard for helpful advice, and to Mr G. L. Lush, H.M. Coroner, for permission to report this case.

J. A. Lourie*, H. C. Drysdale and E. J. C. Wynne
Princess Margaret Hospital, Swindon
* Present address: Nuffield Orthopaedic Centre, Headington, Oxford OX3 7LD.

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Hypertension due to Ask-Upmark Kidney

J. D. SOBEL, N. HAMPEL, A. KURSBAUM, O. ADLER and B. GELLEI

Departments of Internal Medicine B, Urology, Radiology and Pathology, Rambam University Hospital, Aba Khoushy School of Medicine, Haifa, Israel

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Hypertension in adults, when accompanied by pyelographic evidence of unilateral renal hypoplasia, is usually suggestive of renal ischaemia due to stenosis of the main renal artery or its major segmental branches. Less commonly, a single hypoplastic kidney may be the result of unilateral pyelonephritis.

In 1929 Ask-Upmark reported 6 patients, 5 of whom were adolescents, with malignant hypertension and congenital segmental hypoplasia of the kidney. The cardinal features of this uncommon syndrome include unilateral and, less commonly, bilateral, segmental hypoplasia characterised by capsular grooves and decrease in the number of pyramids. The hypoplastic areas contain no glomeruli but have thyroid-like tubules and thick-walled arteries.

A 15-year-old girl is described with unilateral renal hypoplasia and severe hypertension. The latter responded poorly to medication but an immediate cure was effected following nephrectomy. Pathological examination of the excised kidney revealed features consistent with those described by Ask-Upmark.

Case Report

A 15-year-old girl was perfectly well until 6 months prior to her admission, when she noticed episodic visual impairment and poor concentration at school. Examination revealed hypertension of 170/110 mm Hg. Despite diuretic therapy, on follow-up the hypertension reached a level of 180/140 mm Hg. There was no family history of hypertension or past history of renal disease. On admission, general examination was completely within normal limits, except for a blood pressure of 170/140 mm Hg. Fundal examination revealed minimal arterial narrowing only. Electrocardiogram and X-ray chest were normal.

The following routine examinations were performed and found to be normal: full blood count, erythrocyte sedimentation rate, urea, creatinine, calcium, phosphorus, liver function tests, V.M.A. and urinary catechol amines. There was a trace of protein in the urine; the 24-hour urine protein excretion was less than 1 g. The urinary osmolality was 951 mmol. and creatinine clearance was 125 ml/min.

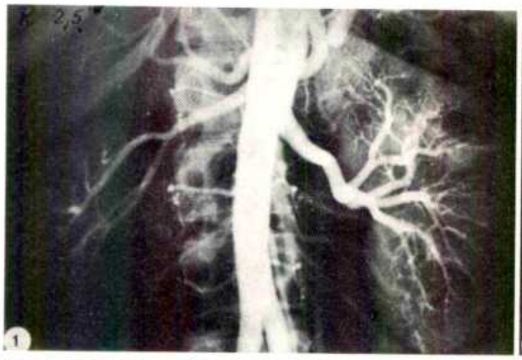
Intravenous pyelogram showed a small right hypoplastic kidney with slightly lobulated borders. Dye excretion was normal and equal on both sides. There was no abnormality of the collecting system including the ureters and bladder. The length of the right kidney was 7 cm, whilst that of the left kidney was 12 cm. Renogram examination was normal.

Selective renal angiography (Fig. 1) revealed a normal left kidney and diffuse hypoplasia of the right kidney. The main renal artery on the right was narrower and smaller than that of the opposite side, but proportionally normal to the reduced kidney mass it was supplying. The nephrogram phase of the angiogram suggested lobulation of the hypoplastic kidney (Fig. 2) During this examination blood was taken from both renal veins for renin estimation: left renal vein 1·71 ng/ml/hr; right renal vein 1·98 ng/ml/hr; peripheral blood renin was 1·55 ng/ml/hr (normal 1·05 ng/ml/hr ± 0·53 S.D.). Renin detected in the aorta was 1·41 ng/ml/hr. These values were obtained whilst the patient was on a normal salt diet and with simultaneous sodium excretion in the urine of 76 mmol/24 hr.

Initially, conservative measures to control the hypertension were advocated: diuretics, propranalol and hydrallazine were administered with little success until it became apparent that the girl had not taken and could not take medication reliably. Surgery was undertaken and the hypoplastic, grooved right kidney was removed. Within 2 weeks of the operation the blood pressure was normal and has remained so during the 6 month follow-up period.

Specimen

The hypoplastic kidney weighed 60 grams and in the vicinity of the upper pole were a number of irregular, depressed grooves. The renal artery, vein and ureter were normal. The fibrous capsule was easily removed. On cutting the



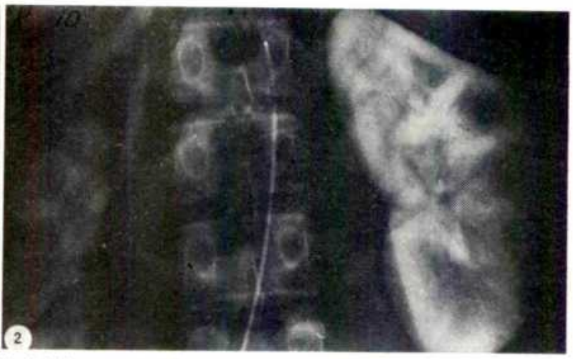


Fig. 1. Selective renal angiography demonstrating normal left kidney and diffuse hypoplasia of the right kidney.

Fig. 2. Nephrogram phase of angiogram.

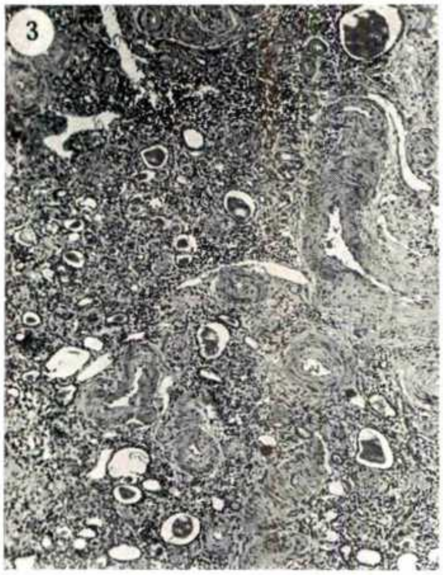
kidney, the macroscopic appearance was normal apart from a number of hypoplastic areas related to the previously described grooves. *Histologically*, the kidney was normal except for the hypoplastic areas. These areas were composed predominantly of atrophic as well as dilated tubules filled with colloid casts resulting in a thyroid-like appearances (Fig. 3). There were also an unusual number of medium-sized arteries with hypertrophic media and fibroelastic thickening of the intima (Fig. 4). A few isolated glomeruli were also present at the periphery of the affected areas. The main renal artery showed a marked thickening of the internal elastic lamina and very thin fibrous intimal cushions.

Discussion

Since the original description in 1929 by Ask-Upmark, there have been several reports of the syndrome of segmental hypoplasia of the kidney and hypertension (Royer *et al.*, 1971; Meares and Gross, 1972; Fikri, Hanrahan and Stept, 1973; Batzenschlager, Weill-Bousson and Guerbaoui, 1974). The renal anomaly, considered to be congenital, consists of transverse grooves on the cortical surface of an hypoplastic kidney and an abnormally small number of pyramids. Histologically, beneath the grooves, the hypoplastic parenchyma contains thyroid-like tubules, thickened arteries and no normal glomeruli. The hypoplasia may be unilateral or, less commonly, bilateral and furthermore, segmental hypoplasia may affect a single area of the kidney or, in the presence of multiple grooves, result in severe hypoplasia.

The diagnosis is suggested by the early onset of hypertension, often severe; occasional proteinuria and, depending on the severity and distribution of the hypoplasia, impaired renal function in approximately half of the patients (Fikri *et al.*, 1973). Intravenous pyelography usually reveals hypoplasia of the affected kidney and thinning of the cortex with some degree of calyceal dilatation. Renal angiography offers the best method of preoperative diagnosis of segmental hypoplasia, revealing a normal renal artery proportional to the dimensions of the kidney and one or more notches may be seen on the surface of the kidney. This latter finding is not always present on angiography and depends on the severity and site of segmental hypoplasia. Accordingly, in some cases of Ask-Upmark, the diagnosis may be made confidently on the basis of pyelographic and angiographic investigations: in others, however, the only abnormal finding on pyelogram and angiogram is of hypoplasia, in no way different from that caused by renal artery stenosis, unilateral pyelonephritis or other forms of congenital dysplasia.

In the patient described, severe hypertension was present, of recent onset and with normal renal function. Renin estimation, together with the normal angiographic appearance of the renal artery excluded extrarenal vascular stenosis: however, the intravenous pyelogram and renal angiogram were in no way diagnostic of the Ask-Upmark kidney. Nevertheless, both the macroscopic and histological findings are typical of those described by Ask-Upmark, and no evidence of pyelonephritis was found.



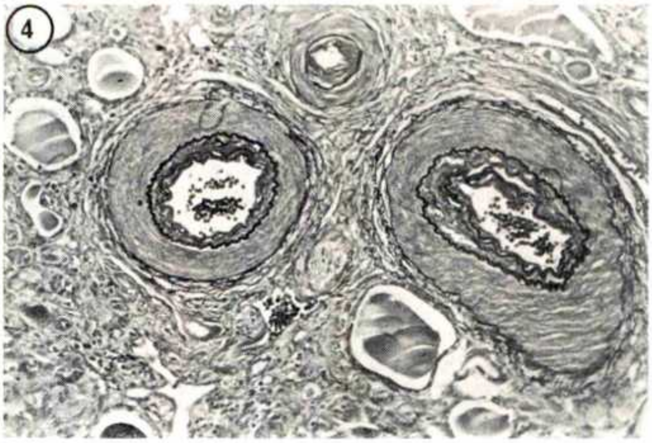


Fig. 3. Scarred area showing atrophic dilated tubules filled with colloid casts: thick-walled arteries and interstitial lymphocytic infiltration (×45 H.E.).

Fig. 4. Arteries with hypertrophric media and fibro elastic thickening of intima.

The pathogenesis of hypertension in the Ask-Upmark kidney is by no means clear. Since nephrectomy may cure the hypertension, it seems unlikely that the hypoplastic kidney failed to produce vasodilator substance such as prostaglandins or a phospholipid renin inhibitor (Lee, 1972). It is more reasonable that the shrunken kidney produces a vasoconstrictor substance and that the removal of the kidney or the atrophic segment reverses the process and reduces the hypertension (Muirhead, *et al.*, 1966). Accordingly, it was natural to suspect the renin-angiotensin system, especially since some authors have described hyperplasia of juxtaglomerular cells in the adjacent normal tissue (Meares *et al.*, 1972). Renin studies have, however, been extremely variable and inconclusive, although elevated levels have been reported (Royer *et al.*, 1971; Godard, Vallotton and Broyer, 1973).

The finding of normal renal vein renin levels in the patient described does not exclude complicity of the renin angiotensin system since renin was measured only under basal conditions. No attempt was made to stimulate renin secretion by means of sodium deprivation, diuretic administration or change in posture. It has been pointed out that a considerable number of subjects with renin-dependent hypertension may be missed if no attempt is made to stimulate renin secretion actively during collection of renal vein samples (Laragh, 1973). Laragh (1976) has recently stressed the continuing difficulties in the laboratory determination of plasma renin activity and pointed out that the finding of normal renin levels does not exclude renin participation in the pathogenesis and maintenance of hypertension, as evidenced by the clinical response to drugs that reduce renin activity.

Prediction of surgical cure is difficult and, as yet, no preoperative tests exist comparable to the use of saralasin in renovascular hypertension. Saralasin, an octapeptide competitive analogue of angiotensin II, lowers the blood pressure in renin dependent hypertension in patients with high plasma renin activity, *i.e.* with renovascular, essential or malignant hypertension (Case *et al.*, 1976). However, saralasin is still in the experimental stage: its use has not been described in the Ask-Upmark kidney and it has been associated with some false positive and negative results (Pettinger and Mitchell, 1975).

Factors which favour a successful outcome of surgery, as outlined by Royer *et al.* (1971), include:

(*a*) radiological evidence of unilateral lesion with compensatory hypertrophy of the opposite kidney;
(*b*) recent onset of the hypertension;
(*c*) absence of advanced hypertensive retinopathy;
(*d*) normal renal function tests.

The patient described fulfilled all the criteria for anticipated surgical cure and when it became apparent that she was unreliable in taking medication, surgery was undertaken with prompt reduction in blood pressure and within a few weeks it had returned to normal levels.

Summary

A young girl in whom severe hypertension was cured by the surgical removal of a unilateral hypoplastic kidney (Ask-Upmark kidney) is described.

The clinicopathological features of the Ask-Upmark kidney are described with particular reference to the aetiology of the hypertension as well as the selection of patients for surgery.

No abnormality of the renin-angiotensin system was detected.

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The Authors

J. D. Sobel, MRCP(UK), FCP(SA). Lecturer Internal Medicine, Aba Khoushy School of Medicine
N. Hampel, MD. Department of Urology, Rambam Medical Centre
A. Kursbaum, MD. Registrar, Department of Internal Medicine B, Rambam Medical Centre
O. Adler, MD. Department of Radiology, Rambam Medical Centre
B. Gellei, MD. Professor of Pathology, Aba Khoushy School of Medicine

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Ectopia in Unduplicated Ureters in Children

P. KESAVAN, M. S. RAMAKRISHNAN and R. FOWLER

The Institute of Child Health and Hospital for Children, Madras, India; and the Royal Children's Hospital, Melbourne, Australia

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Despite their rarity (Burford, Glenn and Burford, 1949; Ellerker, 1958), ectopic unduplicated ureters in children deserve more detailed study than they have yet received because of the wide-ranging abnormalities associated with them. They serve as signposts to an underlying embryologic catastrophe which has far-reaching and possibly disastrous end results for various parts of the urinary tract, with added potential for deformities of the anal canal and the genital tract as well.

Mention has been made in most articles on unduplicated ectopic ureters (Johnston and Davenport, 1969; Kesavan and Ramakrishnan, 1973; Mogg, 1974), which have usually comprised only a few case reports, of the dysplastic nature of the kidney and ureter. Deformities of the trigone and bladder neck, especially in bilateral cases (Chun and Braga, 1965; Cox and Hutch, 1966), have also been noted. We believe that genital and anal anomalies, prominent in our series and also mentioned in some other reports (Uson and Donovan, 1959; Johnston and Davenport, 1969), add a new dimension to the problem. So also does the high incidence of abnormalities in contralateral kidneys without ureteric ectopia. These features raise the question of whether an

Table I

Location of Ectopic Orifice

Location	Number of ureters
Bladder neck	6
Urethra	5
Seminal vesicle	1
Vagina	3
Vestibule	2
Unidentified	2
Total	19

Table II

Identification of Orifice

Case No.	Location Right	Location Left	Endoscopy	Operative
1	Vestibule	Vestibule	NP*	
2	Not known	Urethra	− +	−
3	Bladder neck	Bladder neck	+ +	
4	Bladder neck	Urethra	+ +	
5	Vagina	Normal	−	+
6	Vagina	Normal	−	+
7	Vagina	Normal	NP†	+
8	Bladder neck	Normal	−	+
9	Normal	Bladder neck	+	
10	Urethra	Normal	+	
11	Not known	Normal	−	−
12	Urethra	Normal	+	
13	Normal	Urethra	NP‡	
14	Absent	Bladder neck	+	
15	Seminal vesicle	Normal	−	+

+ Successful.
− Failed to localise the orifice.
NP* Not performed because diagnosis was certain on inspection.
NP† Not performed because of equipment failure.
NP‡ Not performed because voiding cysto-urethrographs demonstrated ectopic opening in the urethra.

abnormally developing ureteric bud can modify organogenesis at the tail end of the foetus to a wider extent than has hitherto been thought possible, or whether ureteric bud abnormality is itself only one component of an earlier critical field defect.

Not surprisingly, with such widespread abnormalities, difficulties can be anticipated in the early recognition and precise delineation of all the attendant components of deformity, and in particular of the ectopic ureters themselves. Delay in recognition, uncertainty in localisation of the orifice, and competing priorities in surgical management are but some aspects of the overall problem. Unsalvageability of uretero-renal units, with doubtful normality of the contralateral kidney, means that prognosis must of necessity be guarded. Especially is this so in relation to continence, where early conjecture as to the competence or incompetence of a recognisably abnormal bladder neck can err in either direction.

By reporting the clinico-pathological features and surgical problems encountered in 19 unduplicated ectopic ureters in 15 children, this paper aims to highlight the early difficulties in clinical management and to focus attention on the embryological significance of the condition. Also, some conclusions as to the pathogenesis of associated ureteric dilatation can be drawn.

Patients

This report is based on case records of 19 affected ureters in 15 children from 2 institutions, the Institute of Child Health and Hospital for Children, Madras, India, and the Royal Children's Hospital, Melbourne. Of the Madras patients, 4 have already been reported (Kesavan and Ramakrishnan, 1973). 10 patients from Melbourne and 1 additional patient from Madras are included in the present study.

All children had, either unilaterally or bilaterally, a single ureter which opened in a position other than the lateral end of a normally formed trigone. 2 of the ureters showed incomplete high duplication.

The condition was bilateral in 4 patients and unilateral in 11, affecting the right ureter in 8 and the left in 3. Table 1 gives details of the location of the ectopic orifices.

The sex incidence was 11 females to 4 males. All the bilateral cases were girls.

4 children presented as neonates, 4 below 1 year of age and the rest later, the oldest being 7 years.

In 1 child there was a history of renal duplication in 2 other family members on the mother's side.

Table III

Overall Incidence of Associated Abnormalities*

Organs involved	Bilateral ectopia No. abnormal/No. at risk†	Unilateral ectopia No. abnormal/No. at risk
Kidneys:		
Ipsilateral	8/8	10/11
Contralateral	– –	4/11
Ureters:		
Ipsilateral	8/8	8/11
Contralateral	– –	5/11
Bladder neck	3/4	6/11
Genitalia	3/4	3/11

* See Table IV for variety of individual abnormalities included.

† Absent kidney counted as if present.

Table IV
Observed Abnormalities

Case No.	Kidney	Ureter	Bladder	Urethra	Others	Intravenous pyelogram
1	Bilateral HN and Dys +L duplication	Dilated. L-conjoined	Hypoplastic	Short	Bilateral ectopic vulval openings (see inset)	Poor function bilaterally
2	L. Dys. R. absent	Segmental atresia+ tortuous	Hypoplastic, Diverticulum+distorted bladder neck	Urogenital sinus anomaly+vaginal atresia+absent cervix	ASD+VSD	R. no secretion
3	L. HN. R. HN+Dys	Wide tortuous. Bilateral reflux	–	–	Imperforate hymen	L. HN. R. poor function
4	Bilateral Dys+L. duplication pelvis	Bilateral wide refluxing	Bladder neck wide+ patulous	Short, wide. Urogenital sinus anomaly	Covered anus. Club foot. Prematurity	L. HN. R. poor function
5	R. Small					R. poor secretion
6	Both appear normal	R. dilated				R. poor secretion, ureter wide.
7	R. HN	R. dilated	Bladder neck wide+ patulous	Wide	2 blind vulval pits (see inset)	R. HN+wide ureter
8	R. Dys+ectopic	Bilateral wide+L. reflux				R. no secretion
9	L. HN	L. wide, tortuous	Para-ureteric diverticulum			L. HN and wide ureter
10	R. Dys. L. HN.	L. dilated tortuous bilateral			Para-vaginal cyst	R. no secretion. L. HN+wide ureter
11	R. Dys.					R. no secretion
12	Bilateral HN+L. malrotated	Bilateral dilated+ reflux	Urachus. Deficient muscle. Bladder neck shelving	Double Spinal dysraphism. Covered anus. Cryptorchidism. "Vater" syndrome	Oes. atresia. Hemivertebra	Bilateral HN. L. malrotated
13	L. Dys	L. reflux				L. dysplastic kidney
14	R. absent. L. HN	L. dilated tortuous	Bladder neck distorted	Veru. Absent		R. absent. L. HN wide ureter
15	R. Dys. L. HN	L. Dilated	Bladder neck distorted	Distorted	Cyst of seminal vesicle	R. no secretion. L. HN+dilated ureter. Extrinsic impression of bladder base

+ = also. R = right. L = left. HN = hydronephrosis. Dys = dysplasia. ASD = atrial septal defect. VSD = ventricular septal defect.

Although the children presented for a variety of reasons, all were found to have urinary infection.

The 4 newborns were brought for various reasons; 2 had multiple congenital anomalies including covered anus, 1 was vomiting and 1 had respiratory distress and congestive cardiac failure. None was brought for the direct manifestation of ectopic ureter. The older infants, up to a few months old, were brought with the combination of urinary infection and renal failure. Only the older female children were brought for the consequence of the abnormal opening of the ureter, namely dribbling of urine.

Of the 11 girls, 8 were ultimately investigated for wetting, 1 of them many years after the first presentation. In the remainder, the presentation was either modified by the associated upper urinary tract anomalies or else they presented entirely because of abnormalities in other systems.

Of the 4 boys, 1 was investigated for dribbling. This is unusual. Males more often present with urinary infection, obstruction or an abdominal mass (Williams, 1968), and this was the case in the rest of the boys in this series. However, the dribbling in this boy might have been due to other causes. He had multiple congenital anomalies, including a very thin-walled, hypoplastic bladder and spinal dysraphism.

Diagnosis

The diagnosis can seldom be established on clinical (Case 1) or radiological (Case 13) criteria alone. (Fig. 1.) Endoscopic or operative demonstration of ectopia is usually required, but even then difficulties can be encountered.

Table V

Operative Management, Results and Follow-up

Case No.	Operative management	Results	Follow-up
1	Left ureteric reimplantation	Temporary extravasation of urine—gastroenteritis, dehydration and renal failure: death	1 month
2	Right nephroureterectomy and left ureterostomy	Poor renal reserve: waiting for definitive surgery	1 year
3	Right nephroureterectomy and left ureteric reimplantation	Recurrent urinary tract infection	8 years
4	Temporary bilateral ureterostomy; right nephroureterectomy and left ureteric reimplantation	Continent by day. Nocturnal wetting only. Temporary reflux into left ureter after reimplantation. Spontaneous cessation subsequently	13 years
5	Right nephroureterectomy	Well	11 years
6	Right ureteric reimplantation	Well	7 years
7	Right ureteric reimplantation	Wetting with dry periods: temporary reflux into contralateral ureter	5 years
8	Right nephroureterectomy	Well: reflux into contralateral ureter waiting for definitive surgery	3 months
9	Left ureterostomy	Well: waiting for definitive surgery	1 year
10	Right ureterostomy followed by nephroureterectomy	Well: contralateral ureter showed temporary reflux then spontaneous cessation	7 years
11	Right nephroureterectomy	Well	3 months
12	Right ureteric reimplantation	Wetting	10 years
13	Left ureteric reimplantation	Well	3 years
14	Left reduction ureteroplasty and reimplantation	Recurrent urinary tract infection	14 years
15	Excision of cystic seminal vesicle and ligation of proximal ureter	Well	17 years

Endoscopic Identification

The investigation most contributory to diagnosis in our cases was endoscopy (Table II), although this succeeded in localising the orifice in only 9 of 15 ectopic ureters examined. Endoscopy was not undertaken in 1 bilateral and 2 unilateral cases, for reasons to be stated.

Bilateral Cases

In 1 child with bilateral vestibular ectopia, the orifices were located without endoscopy. In another bilateral case, endoscopy revealed the position of the left orifice only; the right orifice could not be located at all, even during operative exploration, because the lower end was atretic and was avulsed during dissection (Case 2). (Fig. 2.)

Unilateral Cases

In 4 of 11 cases the orifice could be located easily at endoscopy. In 5 only its absence could be noted. In the remaining 2, endoscopy was not carried out, in 1 (Case 6) because of technical problems and in the other (Case 13) because of urethro-ureteric reflux into the ectopic ureter.

Operative Diagnosis

Of the 6 unilateral cases, comprising 5 in whom endoscopic identification was not achieved and 1 in whom endoscopy was not done, it was possible to confirm the diagnosis during operative exploration in 5; 3 orifices were located in the vagina, 1 in the bladder neck and 1 in the seminal vesicle (Table II). Even during operative exploration it was not possible to locate the orifice in 1 patient (Case 11); a catheter passed through the ureter was seen to impinge on the lower posterior vaginal wall but did not enter the vagina. Also, in 1 bilateral case (Case 2) the right orifice could not be located.

Thus, even operative exploration failed to localise the orifice in 2 instances in the series, probably because of a stenotic orifice or an atretic terminal segment.

Pathological Anatomy

Renal Abnormalities

Malformed kidneys were present in 100% of bilateral cases and, in unilateral cases, in 90% of ipsilateral and 36% of contralateral kidneys (Table III). The abnormal kidneys displayed one or more of the following features: dysplasia, hydronephrosis, ectopia, duplication or absence.

Dysplastic kidneys are prone to become infected and the excised specimens in Cases 3 and 4 showed severe chronic pyelonephritis. Contrary to the views so far published (Johnston and Davenport, 1969; Williams and Royle, 1969) that the more distal the orifice the more severe the malformation, the severity of kidney abnormalities found in our series was unrelated to the site of the orifice.

Ureteric Abnormalities

The ureters were found to be pathological in 100% of bilateral cases. In unilateral cases, 72% of ipsilateral and 45% of contralateral ureters were abnormal in that they displayed one or more of the following features: dysplastic dilatation, segmental atresia, reflux or total absence. In 2 unilateral cases the involved ureters appeared normal but were capped by dysplastic kidneys.

Reflux

A considerable proportion of the patients in our series had concomitant reflux. In 3 bilateral cases (excluding vestibular ectopia), reflux was noted in 5 of 6 ureters. In unilateral cases, 3 of the ectopic and 4 of the contralateral ureters admitted reflux.

Dilatation

Prolonged reflux alone is not responsible for ureteric dilatation. It has long been held that an ectopic ureter traversing the bladder-neck region is subjected to sphincteric squeeze (Stephens, 1956) and so becomes obstructed and dilated. A study of bladder-neck ectopia, however, does not substantiate this theory. In our Case 3, for example, both ureters opened at the bladder neck and were dilated but the orifice on one side was gaping and wide, whereas the other appeared normal; gross upper tract damage was found only on the gaping side. In Case 14, with convincing preoperative evidence of distal ureteric obstruction, a non-sphincteric mechanism of extravesical obstruction was found at operation; this was a concertina-type of valvular obstruction of the juxtavesical ureter (Fig. 5). Case 9 showed a large diverticulum at the trigone and bladder neck; it is highly unlikely that the sphincter was able to obstruct the ureteric orifice which lay inside the diverticulum (Fig. 3). In all other types of ectopia in which the ureteric course is extravesical rather than trans-sphincteric, the dilatation of the ureter could not be called obstructive (Cases 4 and 12) (Fig. 4). The dilatation in these ureters seems more likely to be dysplastic than obstructive in origin.

Bladder Neck and Trigonal Abnormalities

The bladder neck and trigone were maldeveloped in 75% of bilateral and 54% of unilateral cases (Table III). In 2 patients with vestibular and urethral ectopia (Cases 1 and 2), both bilateral. the bladder was extremely small, with no definite demarcation defining the bladder-neck region, This anomaly is usually associated with a wide, patulous urethra and genital anomalies.

Associated bladder-neck deformity, although it aids in the early diagnosis of ectopic ureter, implies a very poor prognosis and has been an insurmountable hurdle in therapy, requiring often

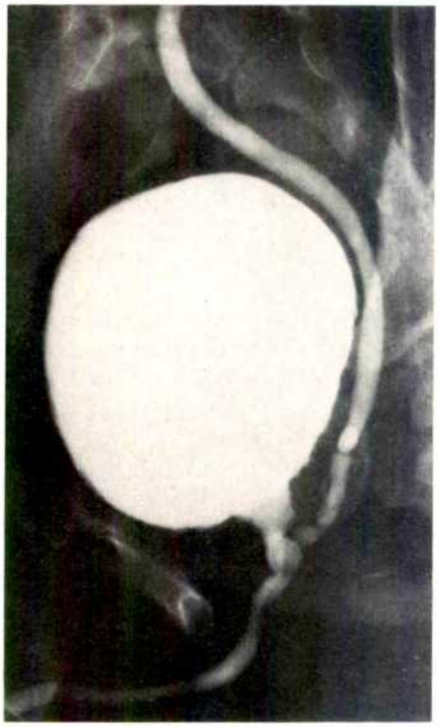

Fig. 1. Case 13—Voiding cysto-urethrogram. Reflux into urethral ectopic ureter.

permanent diversion. This is most often true in bilateral cases, but is not invariably so, as illustrated by the acceptable degree of control in Case 4. Mogg (1974) reported a boy with unilateral ureteric ectopia with hemitrigone, who is continent.

Genital and Anal Anomalies

Genital and anal anomalies were present in 75% of bilateral and 27% of unilateral cases in this series. One boy had a double urethra. 2 others had a covered anus. Case 10 had a pelvic paravaginal cyst which probably arose from the sinus bulbs or the vaginal plate (Hamilton, Boyd and Mossman, 1962). Vaginal atresia was noted in 1 girl and imperforate hymen in another. It is often for these genital anomalies that the children are brought to hospital.

Association of genital and anal anomalies has been noted by other authors. Johnston and Davenport (1969) reported 2 patients with associated rectovestibular fistula and anterior vaginal urethra. Uson and Donovan (1959) reported a case with imperforate hymen. In adult males there are several reports (Engel, 1948; Meisel, 1952; Dickinson, 1963; Schnitzer, 1965) of cystic malformation of the seminal vesicle in association with ureteric ectopia. Testicular hamartoma (Williams and Royle, 1969) and carcinoma (Lange, 1975) were also reported. In 2 of our cases a testis was undescended, 1 being in the abdomen, a situation predisposing to malignancy.

Management and Results

Operative treatment has to be tailored to suit the individual case with its quota of associated abnormalities. Table IV gives details of the various procedures undertaken in our patients and the outcome in respect of urinary tract function. A perusal of this table and of the accompanying synoptic case records will give an idea of the range of radical, conservative and corrective operative procedures which may become necessary. Mention has already been made of the likely need,

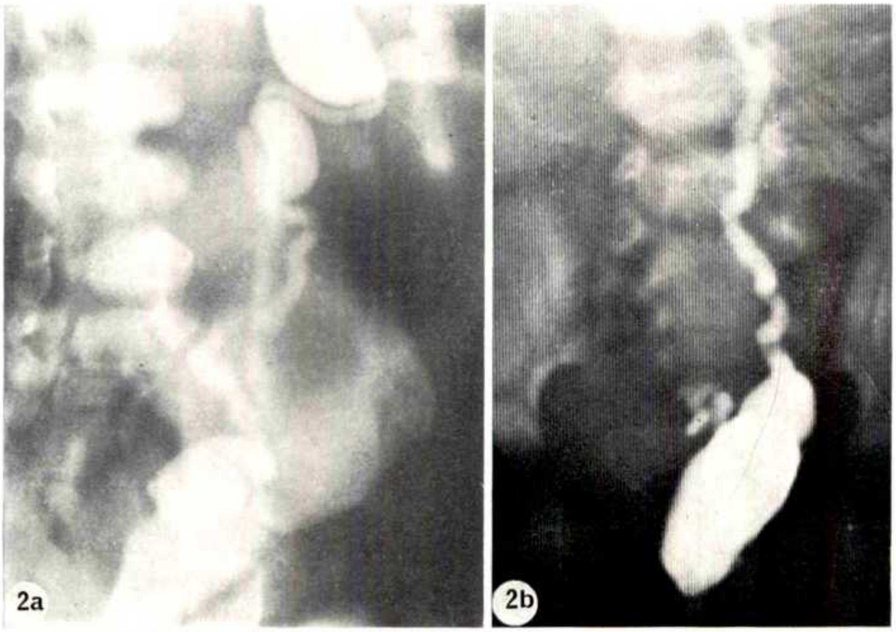

Fig. 2. Case 2—Example of bizarre urinary tract malformations encountered. (a) Intravenous pyelogram. Note the bizarre shape of the left renal pelvis and upper ureter. The calyceal pattern is not clear. (b) Cysto-urethrogram. Note a small eccentric bladder (? left hemi-bladder) with bilateral vesico-ureteric reflux. The right ureter is seen only as a short blind convoluted tubule.

ultimately, for permanent diversion for incontinence due to bladder neck and trigonal insufficiency 3 of our patients are still awaiting definitive treatment, 2 with ureterostomies and 1 with contralateral ureteric reflux.

Nephro-ureterectomy on the ectopic side was carried out in 4 unilateral cases (Cases 5, 8, 10 and 11) and all have continued well after 11 years, 3 months, 7 years, and 3 months respectively. In 3 bilateral cases, unilateral nephro-ureterectomy was carried out, excising a dysplastic and non-functioning uretero-renal unit (Cases 2, 3 and 4).

Ureteric Ligation. In 1 patient with unilateral ectopia in a seminal vesicle and a non-functioning, small kidney, simple ligation of the proximal ureter followed excision of the cystic seminal vesicle. During the procedure the membranous urethra was injured, but recovery after splinting was uneventful. He has been followed up for 17 years and continues well. In difficult situations ureteric ligation may be a compromise alternative to nephro-ureterectomy but is not recommended as a preferred procedure.

Ureteric Reimplantation. Reimplantation of the ectopic ureter to the bladder was carried out in 8 instances, 5 in unilateral cases and 3 in individual ureters in 3 bilateral cases. In 2 of the bilateral cases, contralateral nephro-ureterectomy had been carried out. In the other bilateral case only 1 ureter was operated upon because of the patient's poor general condition (Case 1).

Of the 8 patients in whom reimplantation was carried out, 2 have had no complications. 1 died of pre-renal uraemia following severe gastroenteritis and acute dehydration within a month of surgery (Case 1). 2 patients showed temporary reflux into contralateral ureters which

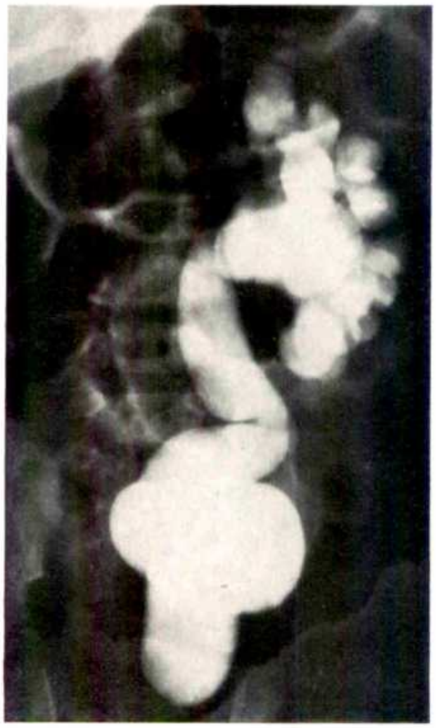

Fig. 3. Case 14—Solitary left ectopic ureter with juxta-vesical obstruction.

ceased spontaneously. Of the 8 reimplanted ureters, 7 later showed no reflux; 1 had temporary postoperative reflux, which later ceased spontaneously.

Residual Disabilities

Disabilities unrelated to surgical complications include reflux into the contralateral ureter, recurrent urinary infection and wetting. Reflux into the contralateral ureter was present before surgery in 1 patient (Case 8). In this child there is a high probability of the reflux ceasing spontaneously since her urine remains infection-free and the reflux is of only mild degree. 2 patients have recurrent or persistent urinary infection (Cases 3 and 14) and are on continuous chemotherapy.

Bladder-neck Repair

3 children have a chronic wetting problem. The probable causes are a defective bladder neck and wide urethra in Case 4, a wide bladder neck in Case 7, and deficient bladder musculature, a distorted trigone and possible neuropathic bladder in Case 12. In Case 4, an attempt was made to repair the bladder neck by a plication procedure, but with only some improvement. Although the girl can keep dry in the day, she still wets at night.

Permanent Diversion

Of the 2 patients with ureterostomies mentioned above as awaiting definitive treatment, 1 demands further discussion. In this girl (Case 2, Fig. 2) with bilateral ectopia, one uretero-renal unit has been excised. The remaining kidney and ureter are so malformed and the bladder is so small that no bladder reconstruction or ureteric reimplantation could be guaranteed to be successful. It seems that permanent urinary diversion in the form of a ureterostomy may prove to be the most satisfactory solution to her problem.

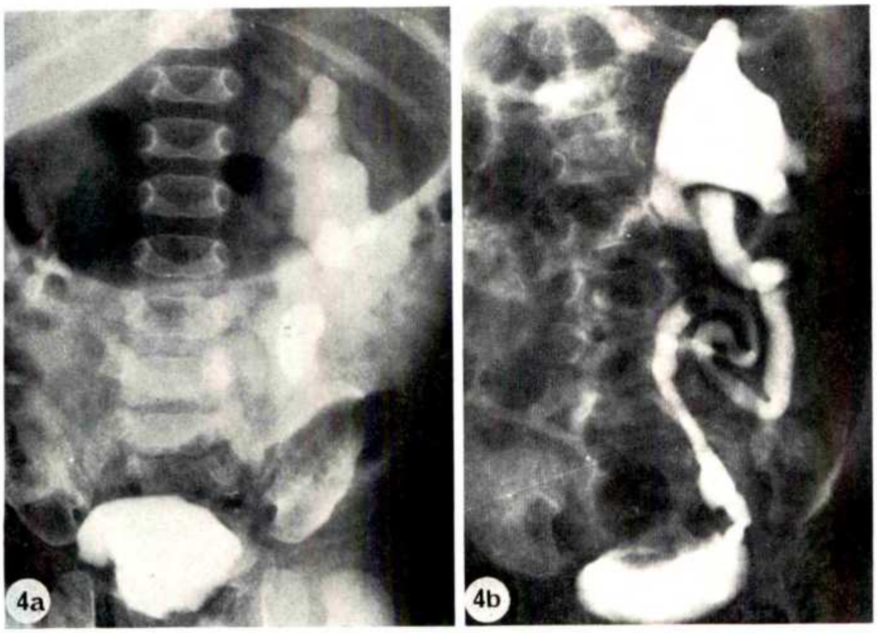

Fig. 4. Case 9—(a) Intravenous pyelogram. Left hydronephrosis and hydroureter with normal right pelvicalyceal pattern. (b) Retrograde pyelogram. Note the highly convoluted dysplastic ureter.

Discussion

Embryogenesis. The Significance of Genital and Anal Abnormalities in Intravesical Ureteric Ectopia

An intravesical ectopic orifice is often considered to be only a minor anatomic variation. Whereas this may be true of double ureters, it is not so with unduplicated ureters, as the cases in this series prove. 5 patients (Cases 3, 4, 8, 9 and 14) had ectopic ureteric orifices in the distal trigone or bladder neck region. Nevertheless, they showed such abnormalities as tortuous refluxing mega-ureters and poorly functioning dysplastic kidneys. Even more striking are the associated genital and anal abnormalities such as imperforate hymen, anterior vaginal urethra and covered anus. The presence of such numerous and wide-ranging abnormalities raises the question as to what possible defects of embryogenesis could have been involved.

The mere presence of ureteric ectopia cannot explain the associated abnormalities. It is well known, for instance, that the ectopic member of a duplex system is often associated with a normal renal segment, whereas this is now shown to be the exception in unduplicated ureters.

It is widely believed that an abnormal ureteric bud can induce abnormal development of the renal blastema. Lower urinary tract abnormalities such as a defective bladder neck or a deficient trigone are believed to be due to maldifferentiation of the terminal segment of the Wolffian duct distal to the ureteric bud which becomes incorporated into the urogenital sinus to form the primitive vesico-urethral canal. Is this maldifferentiation also induced by a defective ureteric bud? If that were the case, one would expect that the more distally the ectopic orifice was placed, the more abnormal would be the lower tract and its neighbouring organs. Some authors, as indicated above, do, in fact, express this concept, which is inconsistent with the findings in the present series, in which the extent and severity of associated abnormalities were unrelated to the degree of caudal displacement of the ureteric orifice.

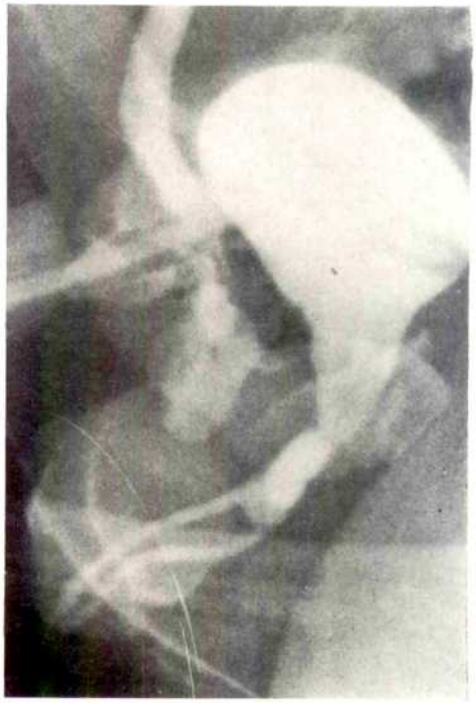

Fig. 5. Case 12—Voiding cysto-urethrogram. Note double anterior urethra, right ectopic ureters with reflux—(balloon cystostomy catheter).

In this series, vaginal, anal and urethral abnormalities, perhaps representing defects of perianal mesodermal migration, have been a prominent feature in cases of ureteric ectopia at the bladder neck, in which caudal displacement of the ureteric orifice is minimal. This raises the alternative question of whether the ectopic ureteric anomaly is a component of a more widespread embryonic field defect rather than just an aberration of ureteric bud development. In support of the latter concept, it should be noted that a high incidence of renal dysplasia, but without associated vesical, bladder neck or genital abnormalities, is encountered with other, more common, types of ureteric bud anomalies, such as megaureters with reflux (Bialestock, 1965), double ureters (Mackie and Stephens, 1975) and para-ureteric diverticula (Wickramasinghe and Stephens, 1977). It would seem that more than an isolated ureteric bud defect is involved in the genesis of ectopia in single ureters.

Diagnostic Difficulties

Diagnosis in older female children is easy because of the typical history of wetting between normal acts of micturition (Yue, 1974). In young infants this sign can be masked by the more obvious and pressing problems of other, overt congenital anomalies or urinary infection. Day-time dribbling with night dryness, so often reported (Williams, 1968), was not seen in this series. Vaginal ureteric ectopia may present with a purulent vulval discharge rather than wetting because the kidney drained is dysplastic and infected and secretes only a small quantity of infected urine (Dean, 1967).

Unlike ectopia in duplicated ureters (Williams, 1954; Simms and Higgins, 1975), there are seldom any signs on intravenous pyelography or on micturating cysto-urethrography which point to the diagnosis of unduplicated ectopic ureter. Especially is this so if the opening is not in the urethra but in the bladder or vagina. In the male, however, urethro-ureteric ectopia can sometimes be clearly demonstrated (Case 13). In bilateral cases, because the bladder is small and relatively empty, the ureter may be seen to end in an unduly caudal position, with an absent or negligible bladder shadow. Excepting these circumstances, the chance of demonstrating unduplicated urethral ectopia by intravenous pyelography or micturating cysto-urethrography is minimal, and endoscopy must form an integral part of the investigation.

One common feature, present in all patients in this series, was urinary infection. Often, in the investigation of urinary infection, routine endoscopy is omitted, especially if reflux is demonstrated. Case 4 illustrates how such a policy delayed the diagnosis of ureteric ectopia. This patient presented in the newborn period with urinary infection and reflux into giant megaureters. She was treated by bilateral cutaneous ureterostomies and chemotherapy and, once the infection was under control, the ureterostomies were closed. Only when the child reported at the age of 5 years with continuous dribbling was endoscopy done and ureteric ectopia discovered. By contrast, in Case 9, where the child was also brought early in life with urinary infection, mega-ureter and reflux, endoscopy was part of the initial investigation and revealed diagnosis early.

Surgical Considerations

Certain technical details are worthy of discussion:

1. There is a small minority of ectopic ureters whose exact termination can only be ascertained during operative exploration. After exposing and opening the extravesical ureter within the abdomen, a probe or a catheter can be passed distally to identify the site of the orifice. However, the instrument may fail to emerge through the orifice if the ureter is atretic or has a small, serpentine tract.
2. Neither a cystic seminal vesicle nor a para-vaginal cyst is easy to excise completely through a conventional lower abdominal incision and the urethra may be injured during the dissection. For this reason, Johnston and Davenport (1969) advocated a posterior, subsacral approach; however, we have had no experience of this technique.
3. Management of the ureteric stump: In cases of urethral and vaginal ureteric ectopia, it is

often advisable to leave the terminal ureteric stump *in situ* to avoid damaging the sphincter muscles. However, we have found it possible in some instances (Cases 10 and 15) to evaginate the terminal portion of the ureter into the urethra or vagina and remove it entirely.

4. Bladder-neck repair: Various methods have been described to narrow the bladder outlet and improve sphincteric function. In only 1 of our patients has such a procedure (Stephens, 1970) been tried, with qualified success. The child is dry in the day for a reasonable length of time although wet at night. Repair of the bladder neck, combined with construction of a urethral sphincter by a levator muscle graft and urethroplasty, has been claimed by Chun and Braga (1965) to give satisfactory continence.

5. Although the smallness of the bladder, so often associated with bilateral ureteric ectopia, can be overcome by augmentation cystoplasty (Williams 1968), any possible gain is likely to be offset by defective sphincter control.

6. Permanent diversion: Permanent urinary diversion is indicated when the bladder is very small and the sphincters incompetent. Often ureterostomy is more suitable than an ileal conduit or ureterosigmoidostomy. Because of the associated renal abnormalities, late complications of intestinal diversion are very likely to develop.

Summary

The clinico-pathological features and surgical management of 19 unduplicated ectopic ureters in 15 children are presented with special reference to the problems of recognition and treatment and to the underlying embryological and pathological significance of the wide-ranging associated abnormalities.

The high incidence of renal and ureteric malformations, both ipsilateral and contralateral, is emphasised, as is also the frequent co-existence of vesical, bladder neck, urethral, genital and anal abnormalities.

These associated anomalies modify the presentation of unduplicated ureteric ectopia and may mask its presence. Late recognition is common, but may be avoided by awareness of the problem.

Whereas the degree of kidney involvement seems to dictate the choice and priorities of surgical treatment, the lower urinary tract anomalies have more significance as regards continuing disability and these largely determine the outcome in relation to continence.

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The Authors

P. Kesavan, MS, MCh, Assistant Professor of Paediatric Surgery, Madras Medical College and the Institute of Child Health and Hospital for Children, Madras, India. Colombo Plan Fellow, Royal Children's Hospital, Melbourne, Australia.
M. S. Ramakrishnan, MS, FRACS, FICS, Professor of Paediatric Surgery, Madras Medical College and the Institute of Child Health and Hospital for Children, Madras, India.
R. Fowler, MD, FRACS, Paediatric Surgeon, Royal Children's Hospital, Melbourne.

Address for reprints: R. Fowler, MD, FRACS, Paediatric Surgeon, Royal Children's Hospital, Melbourne.

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Short Case Report

A Case of Complete Uretero-ileal Fistula

Of all intestino-urinary fistulae, those between ureter and ileum are extremely rare (Scott, 1965; Critchley, 1967; Blumgart and Thakur, 1971). We report a case of fistula between a uretero-ureteric anastomosis and the ileum, with total urinary diversion. A review of the literature indicates this is unique.

Case Report

7 days after abdomino-perineal excision of the rectum for carcinoma, Mr J. N., aged 50, leaked urine from the perineum. An excretion urogram showed a horseshoe kidney and left ureteric injury. An operation to repair the injury was carried out 5 weeks later. The right ureter was initially mistaken for the left (both ureters lay on the left) and was divided low in the pelvis. Reconstruction had to be carried out as illustrated (Fig. 1).

A month later he developed an intestino-urinary fistual (Fig. 2), all urine coming from his colostomy. After intravenous correction of dehydration and acidosis, he remained well with oral sodium bicarbonate and Slow K supplements.

He was readmitted 6 weeks later with peritonitis. Laparotomy revealed a urinary peritonitis due to breakdown of a fistula between the mid-ileum and the uretero-ureteric anastomosis. The ureter below the anastomosis was obliterated. A Boari flap was used in reconstruction and he has subsequently remained in good health.

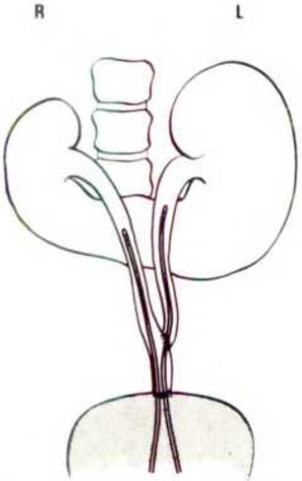

Fig. 1

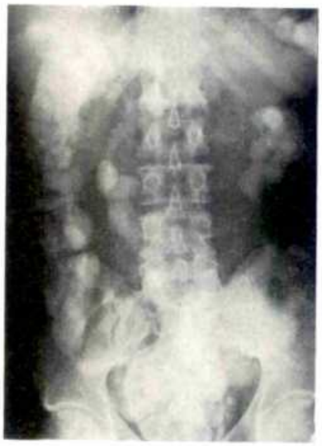

Fig. 2

Discussion

As a result of this experience we recommend that a routine preoperative excretion urogram and operative identification of both ureters are carried out in pelvic surgery.

It was surprising that this patient remained well despite total urinary diversion to ileum. However, other reports show that in the presence of a fistula, renal damage or a major complication will occur and early surgical correction is desirable.

I. Appleyard* and W. Lloyd Jones†
* *Royal Southern Hospital, Liverpool L8*
† *Broadgreen Hospital, Liverpool 14*

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The Results of Urinary Diversion in Multiple Sclerosis

A. D. DESMOND and K. E. D. SHUTTLEWORTH

Department of Urology, St Thomas's Hospital, and National Hospital for Nervous Diseases, Queen Square and Maida Vale

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It has been our custom to use conservative methods of surgery to treat the urological symptoms and complications of multiple sclerosis. By this we mean operations on the bladder and bladder outflow mechanism short of urinary diversion. This attitude was mainly related to our concepts of multiple sclerosis and what we thought would benefit the patient most. Multiple sclerosis differs from other causes of neuropathic bladder in that the condition is associated with other more apparent and seemingly greater disabilities; it produces loss of mobility which considerably impairs the patient's ability to deal with the urinary symptoms, and it is a progressive disease. Thus the maintenance of continence has been that much more difficult to achieve and conservative surgery has only been effective for relatively short periods of time. Even with operations on the bladder such as caecocystoplasty, with or without bladder neck resection or external sphincterotomy, it has often proved impossible to achieve a balance between detrusor power and outflow resistance particularly in the female. We have thus been placed in the position where no satisfactory treatment remains other than urinary diversion. At the same time we have been reluctant to persuade patients with multiple sclerosis to undergo major surgery because of the risks of permanent neurological deterioration secondary to the trauma of surgery and its postoperative complications, and the loss of mobility from prolonged bed rest. There are also certain clinical features often present in this disease which we have deemed contra-indications to urinary diversion. These are decubitus ulceration, faecal incontinence, inability of the patient to manage his or her stoma and advanced neurological disease. On the other hand, there are a significant number of patients to whom we have offered urinary diversion but who have decided, usually for emotive reasons, to persist with a catheter or an appliance. This paper describes our experience of urinary diversion in patients with multiple sclerosis which has shown that the results of surgery have been much better than we had been led to believe.

Patients

Since 1968, 78 patients with multiple sclerosis have attended St Thomas's Hospital for urological assessment. 46 patients underwent surgical treatment; 32 were managed by drugs, catheters or appliances; 12 (15%) were treated by a Bricker (1950) ileal conduit as a method of urinary diversion for persistent urinary incontinence. 20 of the 78 patients have died but none as a result of surgical treatment and 2 have been lost to follow-up.

Of the 12 patients who had diversions, 9 were female and 3 were male; their ages ranged between 20 and 57 although 83% were aged 30 to 50. The duration of multiple sclerosis as judged by the time from the first onset of neurological symptoms varied from 4 to 21 years, while the duration of significant urinary symptoms such as severe urgency or frequency, incontinence or retention varied from 2 to 10 years. The severity of the disease at the time of urinary diversion was graded by the degree of patient mobility. Grade A represented those able to walk reasonably well; grade B represented those who could stand but only walk with crutches or a walking frame; grade C represented those who were chairbound, some of whom could transfer themselves from bed to chair; and grade D included those who were completely dependent on another person for their basic needs and nursing care. The majority (75%) were in grades B and C (Table I).

Management Prior to Urinary Diversion

Prior to urinary diversion. 5 of the 12 patients were being managed by indwelling catheters, the remainder with incontinence appliances. In females, the appliances consisted of plastic pants, sanitary towels and incontinence pads, all of which were generally unsatisfactory. 9 patients had undergone previous surgical treatment which included transurethral surgery in 6 cases, 2 ileocystoplasties with subsequent transurethral surgery and 1 bilateral lower pole nephrectomy for staghorn calculi. The most recent diversion was performed on a patient who had received a urethral sphincter prosthesis following failure of transurethral surgery, but this had also proved to be unsuccessful (Table II).

Indications for Urinary Diversion

The indications for urinary diversion in these patients were severe urinary incontinence which was inadequately controlled by an appliance, inability to tolerate long-term catheterisation due to urological complications or from personal dislike, and failure of other forms of surgical treatment. In particular, 4 patients developed urological complications in spite of treatment which besides endangering renal function were causing further neurological deterioration. These were all infective complications and included 1 man with recurrent attacks of pyelitis and 3 women with severe recurrent cystitis. 6 patients had lost all feeling of both bladder fullness and urethral sensation. Once both modalities are lost, control of continence becomes very difficult to treat. 8 agreed to urinary diversion when it was first offered, 4 of whom indicated that further conservative management was no longer acceptable. One of the men using an incontinence appliance also suffered from pelvic floor and bladder spasms and this, along with the unsatisfactory nature of his appliance, led him to attempt suicide before accepting a diversion.

Results and Complications of Surgery

Following 12 ileal conduit operations, there was no postoperative mortality and the only operative complication was that of primary haemorrhage in one case. 10 patients had postoperative complications (Table III).

It was most important to assess whether a permanent deterioration in the neurological state of the patient had occurred as a result of the operation. 6 felt that no deterioration had occurred, 4 thought there had been a mild deterioration which was of an acceptable degree and 2 suffered a moderate deterioration which had resulted in a permanent reduction in mobility. No obvious correlation was found between the severity of the postoperative complications and the degree of neurological deterioration. No one with an ileal conduit has shown a significant deterioration in renal function although the longest period of follow-up is only 5½ years.

Table I

Presentation

Case No.	Age	Sex	Duration of M.S.	Urological symptoms	Grade	Presentation
1. A. B.	32	M	10	10	B	Retention with overflow
2. S. B.	20	F	6	3	C	Incontinence
3. P. B.	40	F	16	2	C	Incontinence
4. J. C.	41	F	21	3	D	Incontinence
5. E. E.	57	M	11	6	C	Incontinence
6. C. G.	38	F	8	8	B	Retention with overflow
7. L. G.	42	F	8	3	B	Retention with overflow
8. A. M.	41	M	5	5	A	Retention
9. E. N.	46	F	17	3	B	Incontinence
10. J. P.	49	F	12	8	C	Incontinence
11. M. S.	42	F	19	2	C	Incontinence
12. E. S.	45	F	18	9	D	Incontinence and right loin pain

Table II Previous Treatment

Case 1	A. B. Aged 32 Grade B	Male	Presented with incontinence due to chronic retention with overflow. External sphincterotomy performed for spastic external sphincter and paralysed bladder. Incontinence persisted and inadequately controlled by appliance. Catheter resulted in recurrent pyelitis and worsening of M.S. Persuaded to have a diversion.
Case 2	S. B. Aged 20 Grade C	Female	Presented with incontinence due to uninhibited bladder. Bladder stretch and large doses of anticholinergic drugs produced initial improvement only. Refused further conservative management and asked for urinary diversion.
Case 3	P. B. Aged 40 Grade C	Female	Presented with indwelling catheter *in situ* for 18 months. Detrusor muscle showed gross uninhibited contractions so patient was offered a urinary diversion.
Case 4	J. C. Aged 41 Grade D	Female	Presented with incontinence due to an uninhibited bladder. Ileocystoplasty was performed followed by 2 bladder neck resections and an external sphincterotomy for postoperative bladder outlet obstruction. Incontinence persisted and accepted urinary diversion.
Case 5	E. E. Aged 57 Grade C	Male	Presented with incontinence due to an uninhibited bladder associated with bilateral vesico-ureteric reflux, hydronephrosis and impaired renal function. Ileocystoplasty was performed followed by bladder neck resection and an external sphincterotomy for postoperative bladder outlet obstruction. Incontinence persisted and insisted on urinary diversion.
Case 6	C. G. Aged 38 Grade B	Female	Presented with incontinence due to chronic retention with overflow. External sphincterotomy performed for spastic sphincter and paralysed bladder with restoration of continence. Later developed an uninhibited bladder with further outlet obstruction which was treated by bladder stretch with bladder neck resection which produced only temporary improvement. Urethral valve prosthesis inserted which failed due to ulceration of prosthesis into the urethra. Accepted urinary diversion as a result.
Case 7	L. G. Aged 42 Grade B	Female	Developed chronic retention with overflow following a hysterectomy and found to have a paralysed bladder with vesico-ureteric reflux. Bladder neck resection performed but ineffective. External sphincterotomy with a Marshall Marchetti operation produced normal micturition but only for 3 months. Catheter not tolerated and finally accepted urinary diversion.
Case 8	A. M. Aged 41 Grade A	Male	Referred with catheter *in situ* after failed open bladder neck resection for urinary retention. Found to have a paralysed bladder and treated by transurethral bladder neck resection with removal of the lateral lobes of the prostate. Developed further outflow obstruction for which external sphincterotomy was required on 2 subsequent occasions. Incontinence made worse by severe pelvic floor and bladder spasms which were not relieved by drugs, caudal or sympathetic block. Attempted suicide before accepting urinary diversion.
Case 9	E. N. Aged 46 Grade B	Female	Presented with incontinence due to an uninhibited bladder. Bladder stretch and caudal nerve block performed without any subjective improvement. Patient was keen to have a diversion.
Case 10	J. P. Aged 49 Grade C	Female	Incontinence treated for 3 years by an indwelling catheter due to decubitus ulceration. Detrusor muscle showed gross uninhibited contractions and catheter was causing severe recurrent cystitis. Urinary diversion advised while pressure sores were healed.
Case 11	M. S. Aged 42 Grade C	Female	Presented with incontinence following a hysterectomy and found to have an uninhibited bladder. Catheter resulted in recurrent cystitis and worsening of M.S. Keen to have a urinary diversion.
Case 12	E. S. Aged 45 Grade D	Female	Presented with recurrent urinary tract infection, right loin pain and incontinence. A right lower pole nephrectomy was performed for a staghorn calculus. Deterioration in M.S. resulted in gross incontinence associated with an uninhibited bladder and gross bilateral vesico-ureteric reflux. A left lower pole nephrectomy was performed for a staghorn calculus on the left side and this was shortly followed by an ileal conduit.

Table III

Complications following Urinary Diversions

Case No.	Age	Sex	Early complications	Late complications	Neurological deterioration
1. A. B.	32	M	Pyelitis	Incisional hernia Difficulty in managing stoma	Mild
2. S. B.	20	F	Pyelitis Prolonged ileus Pressure sores		None
3. P. B.	40	F		Difficulty in managing stoma	None
4. J. C.	41	F	Prolonged ileus Pyocystis	Unable to manage stoma	None
5. E. E.	57	M		asymptomatic U.T.I.	Mild
6. C. B.	38	F			Mild
7. L. G.	42	F	Pyocystis	Recurrent U.T.I. Excoriation around stoma	None
8. A. M.	41	M	Pyelitis	asymptomatic U.T.I. Haemorrhage from stoma	None
9. E. N.	46	F	Urinary fistula	Difficulty in managing stoma	Moderate
10. J. P.	49	F	Pyelitis Pressure sores	asymptomatic U.T.I.	None
11. M. S.	42	F	Pyocystis	Difficulty in managing stoma	Mild
12. E. S.	45	F	Primary haemorrhage Prolonged ileus	Incisional hernia asymptomatic U.T.I.	Moderate

3 patients have died since their urinary diversion, 1 from progressive demyelination and 2 from bronchopneumonia, but none of them had had further urological problems.

Prevention of Complications

In view of the liability to an increase in morbidity associated with surgery in multiple sclerosis, as shown by these results, much attention to detail is necessary to try to prevent complications. Specialised nursing care is required to prevent pressure sores and to assist in restoring the patient's mobility to its preoperative level. Inadequacy of nursing staff in either experience or numbers should certainly be listed as a contra-indication to elective major surgery on any patient with multiple sclerosis. We now use a LAL (Low Air Loss) bed support system[1] to nurse our multiple sclerotic patients. This has been shown to be effective in the prevention of development of pressure sores and to reduce the nursing requirements of immobile patients (Scales and Hopkins, 1971) and is considerably better than other support systems in reducing the maximum pressures between the patient and the bed (Redfern *et al.*, 1973). Not only does it offer uniform body support removing high-pressure areas, it can also be altered for different postures, allows for evaporation of water and controls the temperature and humidity of the environment. The patient should have intensive physiotherapy in the immediate pre- and postoperative period to prevent joint stiffness and reduction in mobility.

It also seems to be extremely important that the urinary tract is sterile at the time of surgery to reduce the postoperative incidence of pyelitis and purulent cystitis, which were major complications in 7 patients. This is sometimes difficult to achieve because these patients often have chronic urinary tract infection associated with indwelling catheters and resistant organisms, in which case it is mandatory to cover them with intravenous antibiotics during the operation and in the immediate postoperative period. In spite of the need for secondary cystectomy on 3 occasions due to the complication of pyocystis, we do not advocate cystectomy at the primary procedure as this is usually unnecessary and considerably adds to the amount of surgical trauma which is potentially harmful to the patient with multiple sclerosis.

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[1] Marketed by Watkins and Watson Ltd.

The youngest patient (Case 2, S. B.) suffered a marked reduction in mobility following her operation which failed to respond to intensive physiotherapy and large doses of Lioresal. However, a dramatic recovery occurred following a 4-day course of dexamethasone. This has been sustained, resulting in greater mobility than prior to surgery. In view of this experience and the dramatic improvement sometimes noted by neurologists following steroid therapy, it is suggested that the neurological deterioration in multiple sclerosis associated with surgical trauma and its complications may be minimised or even prevented by a course of steroid therapy during the convalescent period at a time when there is no longer any danger of infective complications.

Attitudes of Patients to Urinary Diversion

Opinions as to the efficacy and benefits of an ileal conduit were obtained from the 9 living patients and the spouses of the 3 patients who had died. The 3 spouses and 8 of the patients considered that the operation had been a great success; all of them had or would have recommended the same operation to other patients with multiple sclerosis. 1 man had some misgivings about the operation, but in his case urinary diversion was necessary for urological complications after failure of surgical treatment rather than for relief of symptoms. It had also been noted by the neurologists prior to the operation that he had completely failed to come to terms with any of the disabilities produced by multiple sclerosis, but even he admitted that a stoma was an improvement on a catheter or appliance (Case 1, A. B.). Those who suffered a reduction in mobility found this an acceptable price to pay for cure of incontinence, although 1 patient expressed disappointment to this end (Case 9, E. N.). All the living patients thought that their urological problems had been more distressing than their other neurological disabilities, but this was no longer the case following urinary diversion; all agreed that a urinary stoma and drainage bag was a far better alternative to a catheter or appliance. The change for the better in demeanour and outlook on life was very apparent on interviewing these patients. Of the 12 patients, 4 women and 1 man were participating in a normal sex life. Prior to urinary diversion, 3 of the women had been prevented by an indwelling catheter, and the fourth claimed a considerable improvement as a result of her diversion. The 1 man concerned improved so much following his operation that his sexual potency returned, whereas previously he had been impotent. Of the other 7 patients who had ceased this activity, none had done so as a result of their ileal conduit operation or its complications.

The attitudes of patients with multiple sclerosis who have an ileal conduit are extremely interesting. 8 of the 9 living patients were unable to tell us enough how great had been the improvement in the quality of their lives following urinary diversion. In particular, 3 patients who had initially resisted urinary diversion freely commented that if they had originally appreciated the benefits of a urinary stoma, they would have accepted urinary diversion when it was first offered (Cases 6, 7 and 8). The relatives also commented on the improvement, for they found it made their lives easier too. 1 patient was described by her husband as someone who spent half her life on the lavatory trying to be continent, but since her diversion had become a "normal person" again.

Attitudes of Patients without Urinary Diversion

In view of the apparent success of urinary diversion in the treatment of urinary symptoms of multiple sclerosis, the other patients in this series were asked for their attitudes to the suggestion that their urinary symptoms could also be treated in this way. Out of 78 patients, 20 had died, 2 were lost to follow-up, 9 had ileal conduits and 3 had cerebral involvement and were unable to express an opinion. The remaining 44 who were questioned included 24 males and 20 females. In each case the practical details of managing a urinary stoma, and the possible advantages and disadvantages, were fully explained to the patient prior to obtaining his or her opinion. 6 patients (5 females and 1 male) were interested in having a diversion as part of their future management, none of whom had previously been offered this form of treatment; 9 (7 males and 2 females) would accept diversion if their urinary symptoms got worse; 6 (5 males and 1 female) felt that a diversion would not offer any additional benefit to their existing appliance or catheter; 4 (1 male and 3 females) would not even contemplate the possibility and 19 (10 males and 9 females) stated that they would refuse a diversion if offered one.

This latter group expressed various and often multiple reasons for their refusal, but the most frequent objection was a basic dislike of the concept of a urinary stoma and wearing a "bag", although 7 in this category had permanent indwelling catheters. Other reasons put forward were concern about the possible social stigma attached to wearing a "bag", fear of an operation, the possibility of further deterioration from an operation, worry of ability to manage a stoma, possibility of remission or a cure to multiple sclerosis, loss of femininity and limitation of activities. 3 patients described their lives as a "continuous battle" against multiple sclerosis and accepting a diversion would constitute defeat.

Discussion

The most significant benefit of urinary diversion is the end of incontinence, for there seems to be little doubt that incontinence is often more distressing in terms of loss of human dignity and self-respect than the other neurological disabilities of multiple sclerosis. In women, a urinary stoma means the end of incontinence pads, sanitary towels and plastic pants, and it has considerable advantages over an indwelling catheter. A catheter requires regular changing and sometimes irrigation by trained medical staff; it is liable to block, leak or perish, is commonly associated with recurrent urinary infection by resistant organisms and is generally degrading to one's sense of dignity. A urinary stoma, on the other hand, is easier to conceal, it helps patients to go out with greater confidence, allows women to wear dresses and does not prevent or interfere with sexual intercourse.

In men, the advantages of urinary diversion are more difficult to assess as to some extent the need for diversion depends on the adequacy of the incontinence appliance. Very few of the appliances belonging to the men in this series were of the same type, many were cumbersome, others leaked or did not fit and some had been discarded in spite of incontinence. A urinary stoma was preferred to an incontinence appliance in the 3 men who were diverted.

Indications

Our indications for urinary diversion in multiple sclerosis have not radically altered following this review. They are severe incontinence not effectively controlled by drugs or appliances, intolerance of an indwelling catheter and failure of other forms of surgical treatment. However, in view of the results of surgery and the favourable attitudes of the patients who have had an ileal conduit, we have modified our ideas with regard to timing and attitude to urinary diversion. Firstly, we do not persist with conservative methods of surgery unless they are effective; secondly, we offer diversion as an alternative to a permanent catheter especially in the young and more mobile; thirdly, we accept that incontinence aids in women are generally completely unacceptable and appliances in men often unsatisfactory; and fourthly, we no longer perform ileo- or caecocystoplasty in the multiple sclerotic. We have abandoned these types of cystoplasty as we have found that it has been impossible to adjust the outflow resistance to balance the expulsive power of these bladder substitutions.

The question arises for the surgeon as to what line he should adopt towards the patient who is reluctant to have a urinary diversion when it is indicated. In view of our results, we are now prepared to encourage patients to have this operation whereas previously diversion had often been put forward only as a last resort. The chance of deterioration as a result of the surgical trauma, etc., of course must be explained, but we have shown that with care this danger can be prevented or kept to an acceptable level. To overcome the emotive reasons for refusing a diversion, the doctor and stoma therapist can only explain the facts and the possible advantages it would bring, but undoubtedly the best people to carry out this task are those patients with multiple sclerosis who already have an ileal conduit.

Contra-indications

There is no doubt that an elective urinary diversion should never be carried out in the presence of decubitus ulceration. Apart from the obvious risk of spread of infection at the time of surgery, the dangers of extension and intractability are extremely serious. Not only can these complications cause further neurological deterioration, but there is a very real danger of the patient dying. Of the 20 patients in this series who had died, decubitus ulceration was a major contributory cause of death in 8 of them. In most of these patients, death had been preceded by a rapid deterioration following the development of intractable bed sores. The management of these patients involves highly intensive nursing care and thus we feel that urinary diversion should not be undertaken unless this is available.

Faecal incontinence has always been accepted as a direct contra-indication to urinary diversion. In this review of 78 patients, only 11 (14%) suffered from serious faecal incontinence, 14 (18%) had minor problems—2 or 3 episodes per month—and 18 (23%) developed incontinence only in association with diarrhoea. All but 4 of those with serious problems had advanced disease (Grade D) and were unlikely to be candidates for urinary diversion. Those who had only an occasional episode of faecal incontinence found this far less distressing than urinary incontinence, and incontinence with diarrhoea is fortunately a rare event in multiple sclerosis; in fact, 78% of this series suffered from varying degrees of chronic constipation. In the few rare cases where faecal incontinence cannot be adequately controlled by conservative means, it is always possible for the surgeon to perform a left iliac fossa end colostomy and we have received very favourable reports of this form of treatment.

The prospective assessment that a patient would be unable to manage a urinary stoma has not proved to be a valid contra-indication to diversion. Nearly half (45%) of the 66 patients who had other forms of treatment were assessed as being unable to manage a stoma should it have been offered, and in spite of our preoperative assessment, 50% of those who did have a diversion were unable to change their urostomy bags without assistance. Fortunately almost every patient with multiple sclerosis is extremely well supported either at home by the spouse or family (78% in this series), or in a hospital, nursing home or chronic sick unit (21%). Only 1 patient in this series would have been without help and unable to manage a stoma if urinary diversion had been performed. She was a spinster without any living relatives and living in third part accommodation.

The question as to whether urinary diversion should be performed in patients with advanced neurological disease (Grade D) is controversial both on surgical and emotive grounds. 14 patients in this category were reviewed; 2 had an ileal conduit, 3 had deteriorated mentally and were unable to express an opinion, 5 were satisfied with an appliance and 3 with a catheter, but only 1 man, who had a suprapubic cystotomy, expressed interest in diversion. These findings suggest that in advanced disease, incontinence can be satisfactorily managed by means of a catheter or appliance and urinary diversion should be reserved for the treatment of urological complications where other treatment has failed in those who are mentally alert.

From this series it is statistically not possible to draw any conclusions about the importance of age on the indications for urinary diversion in multiple sclerosis. Only 12 diversions have been performed and over 80% of these were aged 30 to 50, but there was no obvious correlation between age and morbidity.

Summary

Out of a total of 78 patients with multiple sclerosis who underwent urological assessment, 12 (15%) were treated by ileal loop diversion.

The results of surgery were highly satisfactory in spite of a high incidence of postoperative complications.

The surgical trauma that occurs from the operation does not necessarily result in neurological deterioration of the patient.

The only absolute contra-indication to urinary diversion is decubitus ulceration.

Urinary diversion should be considered much earlier in the treatment of incontinence in multiple sclerosis rather than offered as a last resort.

We would like to thank the Multiple Sclerosis Society for the financial support that made this work possible, the neurologists at the National Hospitals at Queen Square and Maida Vale for access to their records and to Mr M. I. Bultitude for supplying the information obtained from micturating cystometrograms.

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The Authors

A. D. Desmond, FRCS, Surgical Registrar, Department of Urology, St Thomas's Hospital.

K. E. D. Shuttleworth, MS, FRCS, Consultant Urologist to St Thomas's Hospital and the National Hospital for Nervous Diseases, Queen Square and Maida Vale.

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Back-flow from Urinary Collecting Devices into the Ileal Conduit

B. BERGMAN, A. E. NILSON, S. PETTERSSON and T. SUNDIN

Departments of Urology and Radiology I, Sahlgrenska sjukhuset, University of Göteborg, Göteborg, Sweden

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Bacteriuria is frequently observed in patients with ileal conduit diversion (Needham, Smith and Matsen, 1970; Guinan *et al.*, 1972). An important factor for the pathogenesis of infection is stagnation of urine secondary to an outflow obstruction from the conduit or to reflux to the upper urinary tract. In a patient with ileal conduit diversion reflux might occur at two different levels, from the conduit to the ureters (Jude, Lusted and Smith, 1959; Lusted *et al.*, 1959; Campbell, Oliver and McKay, 1965; Nogrady, Petitclerc and Moir, 1969), and from the collecting device to the conduit. Demonstration of a back-flow of contrast medium at the latter level would imply that infected urine from the device might be carried into the conduit, from where it might also be conveyed to the upper urinary tract. This possibility does not seem to have been discussed previously in the literature.

The aim of the present investigation was to study the frequency of and the conditions required for a back-flow from the collecting device into the conduit in patients with ileal conduit diversion.

Patients and Methods

The present study was intended to be performed in the 51 surviving patients living in Göteborg and who were operated upon with ileal conduit diversion at our clinic during the period 1963 to 1973. 5 patients were excluded, 3 because of poor general condition and 2 because they refused to participate in the investigation. The remaining 46 patients (31 men and 15 women, mean age 60 years, range 27 to 76 years) were studied after a mean postoperative period of 32 months (range 3 months to 9 years). The examinations were performed when the patients were admitted for their routine controls.

The indication for urinary diversion was malignant disease in 38 patients (urinary bladder tumours 32, gynaecological tumours 3, urethral cancer 2, rectal cancer 1) and benign disease in 8 patients (neuropathic bladders 4, bladder exstrophy 3, recto-vesical fistula 1).

The uretero-intestinal anastomoses were performed with an open end-to-side technique which did not aim to prevent reflux (Cordonnier, 1949; Sundin and Pettersson, 1974).

Definitions. The cutaneous ileal stoma was classified as a *nipple* stoma when it protruded 2 cm or more above skin level with the patient in the supine position and as a *flat* stoma when it protruded less than 2 cm. A stoma which easily allowed catheter size 18 F to pass was called a *wide* stoma, those which did not were designated as *narrow* stomas.

Radiological Examinations. The patients were instructed not to eat or drink after 9 p.m. the day before the radiological examination. The contrast medium used was a solution of sodium-metrizoate (Isopaque Cysto®, Nyegaard, 100 mg I per ml) supplied in sterile infusion-sets and warmed to 37°C (density 1·1 g per ml, viscosity 0·96 CP).

Frequency Studies. The frequency of back-flow from the urinary collecting device into the ileal conduit was studied in the total material of 46 patients (Table I). 42 of them had a flat stoma, 37 being wide and 5 narrow. The remaining 4 patients had a nipple stoma, all of which were wide.

A urinary collecting device (volume 600 to 800 ml) without a non-return valve was used in all patients in the study. At the beginning of the examination the device was filled with 500 ml of contrast medium. The patients were instructed to carry out a certain programme of physical activity as follows: to turn once on to each side in the supine position, to sit up twice, and to walk around for 10 minutes. Each of these activities was immediately followed by X-ray of the conduit and the upper urinary tract with the patients in the supine position, slightly turned to eliminate overprojection of the contrast-filled device.

In order to study the influence of different volumes in the device on the frequency of back-flow, all patients in whom a back-flow was demonstrated at 500 ml were reinvestigated on another day with smaller amounts of contrast medium in the device. At this re-examination gradually increasing volumes of 200 ml, 300 ml and 400 ml were used.

Table I

Cumulative Frequency of Back-flow from the Collecting Device to the Ileal Conduit at Different Degrees of Device Filling in relation to the Type of Stoma

	Contrast volume in the device (ml)	Flat stoma		Nipple stoma
		Wide	Narrow	Wide
Number of patients *with* back-flow at	200	0	0	–
	300	2	0	–
	400	4	0	–
	500	7	2	0
Number of patients *without* back-flow		30	3	4
Total number		37	5	4

– = Not examined.

Table II

Back-flow from the Cylinder to the Ileal Conduit at Different External Pressures in relation to the Type of Stoma

	Extra-abdominal pressure (cm H_2O)	Flat stoma		Nipple stoma
		Wide	Narrow	Wide
Number of patients *with* back-flow at	0–5	6	0	0
	6–10	3	1	0
	11–15	–	3	0
	16–25	–	–	1
	26–35	–	–	1
Number of patients *without* back-flow		0	0	1
Total number		9	4	3

4 patients with back-flow to the conduit were re-examined 1 to 3 times with a device provided with a non-return valve.

Pressure Studies. The extra-abdominal pressure necessary to cause a back-flow of contrast medium from the device through the stoma and into the conduit was studied in 16 patients (Table II). 13 patients, who were chosen at random, had a flat stoma, 9 being wide and 4 narrow. In 3 of these 13 patients back-flow from the device had been demonstrated in the frequency study. Also, 3 patients with a wide nipple stoma were investigated.

With the patients in the supine position, a plastic cylinder with a diameter of 5 cm was pasted so as to obtain a watertight fit around the stoma. Contrast medium was added intermittently to the cylinder every 2 minutes in such a way that the height of the contrast medium column increased by 2 cm each time. The conduit and the upper urinary tract were monitored by fluoroscopy and filmed intermittently. The height of the contrast medium column was noted at the moment when contrast medium entered the conduit and the investigation was then concluded. As long as no back-flow was observed the height of the column was increased to a maximum of 32 cm (equivalent to a pressure of 35 cm H_2O).

Statistical Methods. Differences between groups were analysed with the two-tailed Wilcoxon–Mann–Whitney test and four-fold test (Documenta Geigy).

Results

Frequency of Back-flow from the Device. Back-flow of contrast medium into the ileal conduit occurred in 9 of the 42 patients with a flat stoma (21 %) when the collecting device was filled to a volume of 500 ml (Table I). Back-flow to the conduit did not occur when these 9 patients were

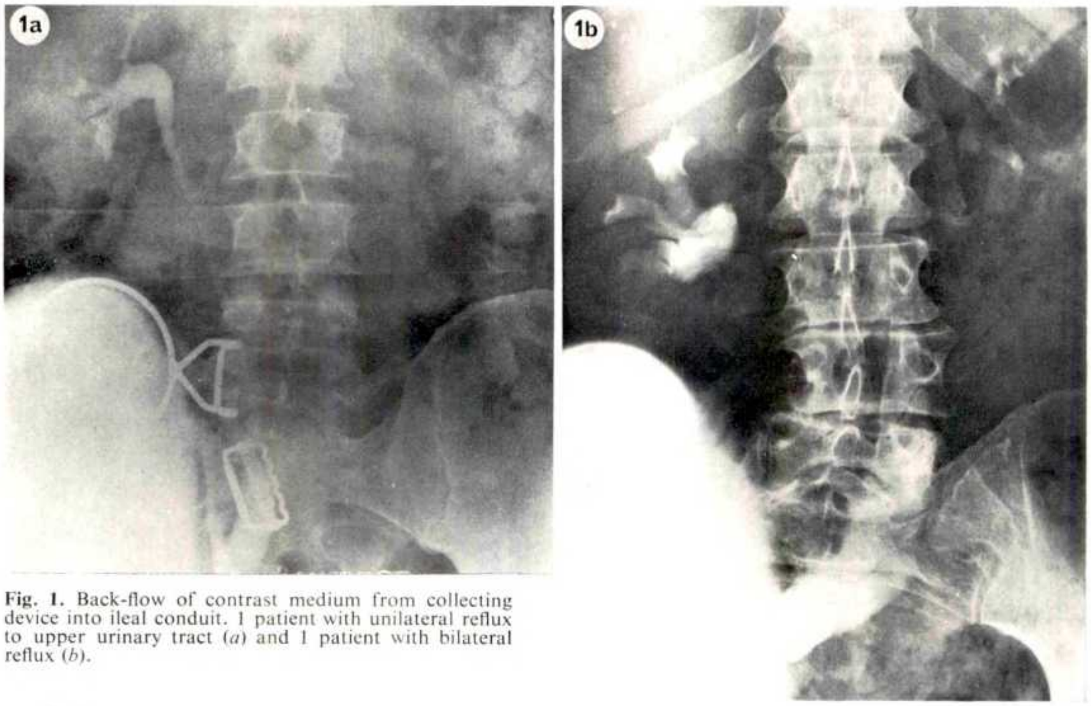

Fig. 1. Back-flow of contrast medium from collecting device into ileal conduit. 1 patient with unilateral reflux to upper urinary tract (*a*) and 1 patient with bilateral reflux (*b*).

reinvestigated with 200 ml in the device. When the volume was increased to 300 ml back-flow was registered in 2 patients, and with a volume of 400 ml in a total of 4 patients. Back-flow occurred not only to the conduit but also to the upper urinary tract in 6 of these 9 patients (Fig. 1*a* and *b*). Back-flow from the collecting device into the conduit was not observed in any of the 4 patients with a nipple stoma.

A back-flow could be registered in all 4 patients, in at least 1 of the 1 to 3 investigations, when 4 of the 9 patients with back-flow were re-examined with a non-return valve device.

Back-flow in Relation to Extra-abdominal Pressure. The pressures causing back-flow of contrast medium from the cylinder to the conduit are given in Table II. The contrast medium flowed from the cylinder into the ileal conduit at pressures below 16 cm H_2O in all the 13 patients with a flat stoma. Back-flow occurred at pressures of 0 to 5 cm H_2O in 6 out of the 9 patients with a wide flat stoma and at pressures of 6 to 10 cm H_2O in the other 3 patients. The corresponding pressures were 7, 12, 13 and 13 cm H_2O in the 4 patients with a narrow flat stoma. These values are significantly higher than the pressures necessary for back-flow through a wide flat stoma ($P < 0{\cdot}05$).

3 of the 16 patients in this study had had a demonstrable back-flow from the device into the conduit in the frequency study. The hydrostatic pressures (3, 7 and 9 cm H_2O) necessary for the contrast medium to flow from the cylinder into the conduit did not differ significantly from the pressures needed in the other patients tested with the cylinder.

The contrast medium flowed from the cylinder into the conduit in 2 of the 3 patients with a nipple stoma at pressures of 25 and 35 cm H_2O, while no contrast medium flowed into the conduit in the third patient. All nipple stomas resisted back-flow of contrast medium into the conduit better than any flat stoma, whether wide or narrow ($P < 0{\cdot}05$).

Discussion

In the present study 21 % of the patients with a flat stoma had a demonstrable back-flow from the collecting device into the ileal conduit after moderate physical activity. This figure is to be regarded as a minimum as the contents of the device did not always reach the stoma level during the activities studied. The fact that back-flow was observed in 15 out of 16 patients tested with the fluid-filled cylinder pasted around the stoma suggests that back-flow may occur more frequently during everyday physical activity and during sleep.

Back-flow to the conduit was usually observed at pressure not exceeding 10 cm H_2O. This low-pressure back-flow into the conduit, and sometimes also to the upper urinary tract, may contribute to the high frequency of urinary tract infection observed in patients with ileal conduit diversion (Jude *et al.*, 1959; Lusted *et al.*, 1959; Campbell *et al.*, 1965; Nogrady *et al.*, 1969).

The frequency of back-flow increased with the amount of fluid in the device. These patients should therefore be recommended to empty their collecting device frequently or to have it connected to a uribag. A uribag should always be used during the night. Tight clothing, which may compress the device and bring fluid up to the stoma, should be avoided.

It might be argued that the high frequency of back-flow observed in the present study could have been prevented by using a non-return valve device. However, in the 4 patients examined with both types of device a back-flow was observed with both. Thus, the valve seems to function poorly in at least some types of devices.

Construction of a flat stoma of the ileal conduit has been recommended by some authors (Bricker, 1950; Malek, Burke and DeWeerd, 1971; Lapides, 1971). A nipple stoma has, on the other hand, been recommended by others in order to decrease the incidence of stomal strictures, to protect the skin and to facilitate changing of the collecting device (Stamey and Scott, 1957; Johnston and Rickham, 1958; McEwan and Clark, 1973). Turnbull and Higgins (1957) found that an ileal nipple of 5 cm in length in uretero-ileo-sigmoidostomy resisted back-flow from a barium enema. These results are in accordance with the findings in the present study in which it was demonstrated that a wide cutaneous nipple stoma resisted back-flow significantly better than both narrow and wide flat stomas.

Summary

The occurrence of back-flow from urinary collecting devices into the ileal conduit was observed in 9 out of 46 patients. In 6 of them back-flow to the upper urinary tract also occurred.

Nipple stomas of at least 2 cm height were found to resist back-flow into the conduit better than any flat stoma.

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The Authors

B. Bergman, MD, now Assistant Head, Department of Urology, University of Umeå, Umeå.
A. E. Nilson, MD, Head, Department of Urologic Radiology, Sahlgrenska sjukhuset, Göteborg.
S. Pettersson, MD, Associate Professor, Department of Urology, Sahlgrenska sjukhuset, Göteborg.
T. Sundin, MD, now Professor of Urology, Department of Urology, University of Lund, Lund.

Correspondence to: Bo Bergman, Department of Urology, University of Umeå, Umeå, Sweden.

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Short Case Report

Common Iliac-Ileal Conduit Fistula

Complications at the blind end of ileal conduits are uncommon, usually occurring at the uretero-ileal anastomosis. Fistulous formation between conduit and iliac artery is very rare. A case is described following correction of stenosis at the uretero-ileal junction.

Case Report

Mrs I. P., age 54, attended in February 1976 following a total cystectomy and ileal conduit for carcinoma of the bladder in January 1975 at another hospital. The ureters were implanted separately into the conduit. She was asymptomatic but on investigation was found to have a non-functioning left kidney with right-sided hydroureter and nephrosis. No reflux was demonstrated. An M.S.U. cultured *E. coli* and her blood urea was 3 times normal. Exploration was advisable in view of deteriorating renal function and onset of loin pain.

A paramedian incision was used. Dense adhesions were found, the blind end of the conduit was impossible to mobilise. The right ureter was identified above the pelvic brim but not traced distally, therefore divided and reimplanted using a sialastic splint. The left ureter was never identified, but in the course of the dissection 2 holes were made in the common iliac artery, which were repaired with 40 ethyflex. She was discharged 10 days after operation.

3 weeks later she developed pulsatile bleeding from the conduit. It ceased spontaneously after 10 minutes, only to restart 10 hours later. On admission a gauze covered the stoma, but on removal a jet of blood projected several inches into the air. In theatre, following resuscitation, the fistula was found with difficulty and only proximal and distal obliteration of the common iliac artery was feasable to effect haemostasis.

The right limb became ischaemic 10 hours later necessitating a femoro-femoral bypass procedure to save it. This proved successful. However, she developed an entero-cutaneous fistula following the emergency operation from which she died 3 months later.

Comment

Beaugie (1973) reported a similar case and noted the presence of a "warning haemorrhage" as in this case prior to the massive exsanguinating bleed. Fistulous formation 6 weeks after arterial closure was presumably due to low-grade sepsis between the base of the conduit and artery. In this case arterial obliteration followed by a femoro-femoral by-pass proved successful.

J. R. HINDMARSH
Department of Urology, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE.

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A Further Assessment of Bladder Transection in the Management of Adult Enuresis and Allied Conditions

K. F. PARSONS, P. J. O'BOYLE and N. O. K. GIBBON
The Regional Urological Centre, Sefton General Hospital, Liverpool

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Transection of the bladder, with division of all the inferior lateral communications including the inferior vesical vessels, was introduced for the control of uninhibited bladder contractions in 1967 (Turner-Warwick and Ashken, 1967). The operation, designed as a denervation procedure for interstitial cystitis, had been applied with good results to a 58-year-old female with diurnal frequency and urge incontinence in whom uninhibited bladder contractions had been demonstrated. The procedure, however, produced an atonic bladder and bladder-neck resection was necessary to establish satisfactory voiding. Yeates (1970) described the use of bladder transection alone, in the "enuretic syndrome" and in 1973 reported a series of patients with encouraging results and no incidence of atonia (Essenhigh and Yeates, 1973). Gibbon *et al.* (1973) simultaneously published a preliminary report of 7 patients on whom this operation had been used with similar beneficial effects. The latter series has been extended here and the results are presented. A minor modification to the original operation is described.

Patients and Methods

Bladder transection has been performed on 28 patients in the last 4 years. There were 13 male and 15 female, with a mean age at operation of 29·6 years (range 17 to 61).

They were classified into 4 main groups on the basis of symptoms:

(*a*) One patient was a primary enuretic without daytime symptoms.
(*b*) 14 had the true "enuretic syndrome" with daytime symptoms of inadequate bladder inhibition.
(*c*) 6 with frequency and urge incontinence had originally been enuretic, with conversion to nocturia in their teens. 2 further patients included in this group had never been enuretic, but had lifelong nocturia, with daytime frequency and urgency.
(*d*) 5 were considered to be neuropathic enuretics with evidence of neurological disease in association with their bladder symptoms.

These patients all had severe and, in many cases, lifelong symptoms, as a consequence of which their social and personal lives were disrupted to the extent of broken engagements or marital separation. The operation was only contemplated after a failure to respond to standard medical treatment, and in 6 patients overdistension of the bladder had been used without significant improvement. All patients had normal upper tracts on intravenous urography, and sterile urine.

The bladder function was assessed preoperatively in the first 9 patients by simple cystometry. This was performed with the patient supine, and the bladder filled with saline by a 12F transurethral catheter. The pressure changes were measured by a saline manometer. Each of the remaining 19 patients had a full pressure flow urodynamic investigation.

The bladder was filled transurethrally by a 12F Nelaton catheter, alongside which was a 1 mm external diameter pressure catheter. A similar catheter was placed rectally allowing subtraction of the abdominal pressure to determine detrusor function. The technique of rapid filling supine cystometry was employed as a provocative test for deficient bladder inhibition. In doubtful cases the filling cystometrogram was repeated in the upright position. A micturition cystogram was obtained in each patient (the males upright and the females seated), with simultaneous measurement of flow rates. In some cases the study was performed under X-ray control with a videotape recording of the composite television picture of the pressure recordings with the filling and voiding cysto-urethrograph.

Postoperative studies were performed under similar test conditions for comparative purposes.

Operative Technique

The bladder was exposed through a Pfannenstiel incision, and the transection started anteriorly 2 cm from the bladder neck. The incision was continued circumferentially to divide the bladder completely 2 cm above the trigone. In the first 4 patients a bridge of tissue was left over the ureters (Fig. 1a) because of the risk of producing reflux if the submucosal ureteric fibres were unintentionally divided. All the rest had a complete transection (Fig. 1b), and no reflux was produced.

Following the report by Mahoney and Laferte (1972) on the use of myotomy to control detrusor hyperactivity, this modification was added to the standard transection procedure in 7 patients. 1, 2, or 3 incisions dividing all the detrusor syncytial fibres, but not the mucosa, were made across the bladder prior to the transection. The incisions were apposed with catgut sutures to ensure haemostasis, and to prevent herniation of the bladder mucosa (Fig. 1c). In each case the bladder was reconstituted with continuous catgut and drained by catheter for 7 to 10 days.

Results

Pre-operative cystometry

Pre-operative cystometrograms were found to be of 4 types: normal in 4 patients; uninhibited normotonic in 10; uninhibited hypertonic in 6; and sustained hypertonic in 8. The relationship between the cystometrogram and the symptomatology is shown in the Table.

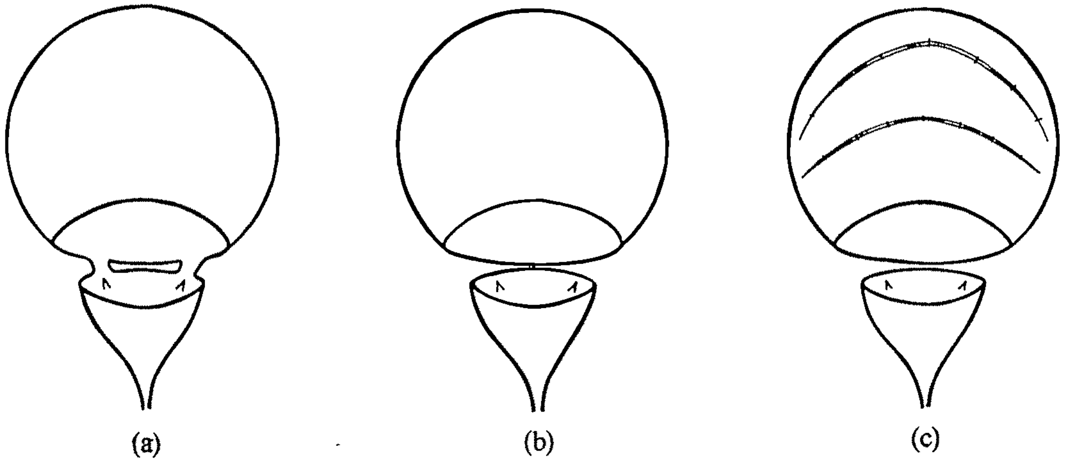
(a) (b) (c)

Fig. 1.

Table

C.M.G.	Enuretic	Enuretic syndrome	Urge incont. with nocturia	Neuropathic
Normal	1	2	–	1
Uninhibited normotonic	–	6	4	–
Uninhibited hypertonic	–	4	2	–
Sustained hypertonic	–	2	2	4

There was no clear correlation between symptoms and the type of cystometrogram, although the sustained hypertonic pattern was seen in all but one of the neuropathic enuretics.

No evidence of obstruction was found in those patients who had a full urodynamic assessment; the flow rates were all within or above normal values. Those patients who had higher flow rates were also found to have slightly elevated detrusor voiding pressures, and could be classified as "supervoiders".

The Effect of the Operation

1. *Enuresis*

17 patients were enuretic prior to the operation. 11 were cured of enuresis postoperatively, being invariably dry throughout the night, and of these 11 only 6 had nocturia.

2. *Daytime Symptoms*

21 patients had urge incontinence. Following transection 14 (66%) were free from leakage during the day. There was also a decrease in the diurnal voiding frequency (Fig. 2). The time between voiding was significantly increased by a mean of 1 hour (S.D. 1 hour 30 min, $P < 0{\cdot}01$). If considered as a separate group, the 7 patients who had an additional detrusor myotomy showed no significant increase in time between voids. (Mean increase 45 min, S.D. 1 hour, $t = 1{\cdot}86$ ns.)

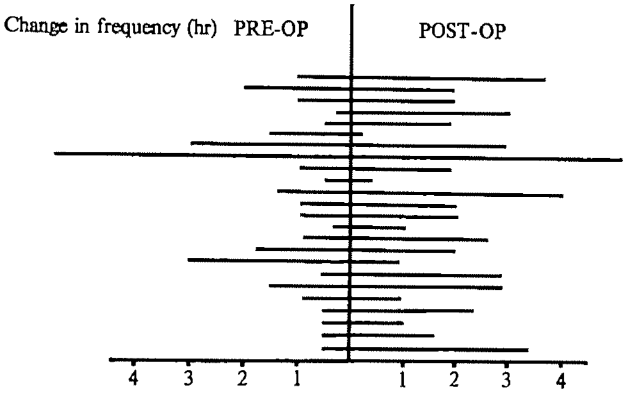

Fig. 2.

3. *Detrusor Function*

22 patients had follow-up urodynamic studies between 3 months and 4 years postoperatively. 5 patients had no change in the cystometric pattern. 3 became completely normal, of whom 2 had previously had uninhibited hypertonic and 1 a sustained hypertonic cystometrogram. 2 patients developed atonic bladders (1 having been normal preoperatively and the other uninhibited hypertonic). The majority of patients (60%), however, retained a similar cystometric pattern but with a shift to the right, the bladders accommodating larger volumes at capacity with a delay in development of higher pressures, either as uninhibited pressure waves or as general hypertonicity.

The operation did not affect flow rates and the relationship between detrusor voiding pressure and flow rates remained unaltered postoperatively.

4. *Bladder Volume*

All but 4 of the patients studied postoperatively had an increase in bladder volume (Fig. 3). This was statistically significant, the mean increase (ml) being 159 (S.D. 125, $P < 0{\cdot}001$). If the 7 patients who had an additional detrusor myotomy are considered separately there was no difference in the increase in volume. (Mean increase 159, S.D. 138.)

5. *Bladder Outline*

The operation had no long-term effect on bladder outline. Postoperative videocystography showed a normal bladder outline both during filling and voiding phases, with normal movement of the fundus throughout voiding.

Discussion

The preoperative urodynamic findings in the present series are similar to other published reports (Torrens and Collins, 1975; Whiteside and Arnold, 1975). The one patient with primary enuresis had a normal cystometrogram while those patients with significant diurnal symptoms showed detrusor hyperactivity.

The control of detrusor hyperactivity is difficult. Chemotherapy, classically with anticholinergic preparations, remains the treatment of choice and is frequently successful in controlling symptoms.

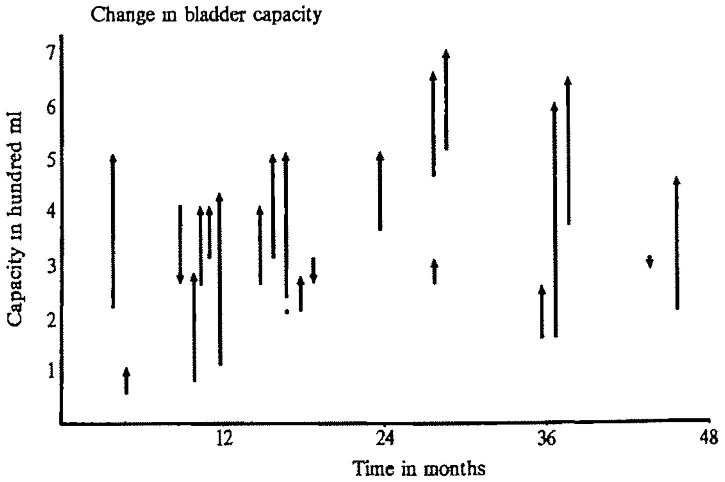

Fig. 3.

Other drugs have been tried with varying degrees of success and a recent report of the use of bromocriptine, a dopamine agonist, appears promising (Farrar and Osborne, 1976). However, a major problem of continuous chemotherapy is that the dose required to produce effective relief of bladder symptoms often results in unwanted side effects which may themselves be unacceptable to the patient.

Recent attempts have been made to control detrusor hyperactivity surgically by selective sacral neurectomy (Torrens and Griffiths, 1974,) and by a modification of the Helmstein procedure of bladder distension under epidural anaesthesia (Dunn, Smith and Ardran, 1974; Whitfield and Mayo, 1975). The latter procedure may have a beneficial effect, though in our experience this is usually of a temporary nature. The 28 patients in the present series had failed to respond to chemotherapy and in some cases bladder overdistension and the persistence of severe bladder symptoms therefore made further treatment desirable. Transection of the bladder, though a major surgical procedure, may provide an effective means of treating this disabling condition.

That the operation has a definite effect on bladder activity is shown objectively by a reduction in daytime frequency, loss of urge incontinence, loss of enuresis and a change in bladder volume. There were, however, 5 patients who did not respond to transection, either symptomatically or as judged by cystometry. In each of these cases the poor response was not predictable by the pre-operative symptom complex or the cystometrogram, although the presence of daytime symptoms with a normal cystometrogram ("sensory urgency"), showed no response in 2 of the 3 cases of this type.

In patients who improved following the operation (81%), the effect may be due to a sensory denervation as the primary effect is upon tone and accommodation during the filling phase, voiding being unaffected. Bladder function, however, does not return entirely to normal post-operatively, since uninhibited pressure waves are still evident, though at increased volumes. Interruption of the detrusor syncytium may also account for this effect of the operation, and for this reason detrusor myotomy was added to the primary procedure in an attempt further to reduce excessive detrusor activity. No obvious benefit was derived from this procedure, however, the increase in bladder volume being the same with or without myotomy, and there being no additional change in the cystometrograms or diurnal symptoms.

The effect of the operation would appear to be prolonged. The increase in volume and change in bladder symptoms have been maintained for 4 years, for example, in the earliest patient in whom 2 repeated urodynamic studies have been performed, both records being identical.

In this series of patients there has been 1 postoperative death at 10 days due to a massive pulmonary embolism. There was, however, no evidence to suggest that this operation is more likely to produce this complication than any other. A 2nd patient required re-exploration due to arterial bleeding at the myotomy sites. These had not been oversewn and haemostasis had appeared satisfactory at the time of operation. Subsequently all myotomies have been reconstituted with 3/0 chromic catgut and no further bleeding encountered.

It is emphasised, therefore, that although this is a relatively simple operation it should be reserved for patients with prolonged and severe bladder symptoms, who have evidence of detrusor hyperactivity, and who do not respond to conservative measures.

Summary

The use of bladder transection for the management of adult enuresis and allied conditions is reported. The beneficial effects of the operation, assessed by an improvement of symptoms and measured objectively by urodynamic investigation, have been found to be maintained during 4 years' experience of the procedure.

The authors would like to thank Mr J. G. Gow, Mr R. M. Jameson and Mr J. K. Rawlinson for permission to study patients under their care.

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The Authors

K. F. Parsons, FRCS, Research Fellow to the Merseyside Association for Kidney Research.
P. J. O'Boyle, FRCSE, Senior Surgical Registrar.
N. O. K. Gibbon, ChM, FRCS, Director, Regional Urological Centre.

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Bladder Transection for Adult Enuresis

J. R. HINDMARSH, D. M. ESSENHIGH and W. KEITH YEATES
Department of Urology, Newcastle General Hospital, Newcastle upon Tyne

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In its most severe form the adult enuretic syndrome is a crippling social disease, greatly restricting the sufferer and frequently causing emotional instability and matrimonial friction.

Little is known of the aetiology of this condition. It is usual to find instability of the detrusor in these patients and treatment is generally aimed at reducing bladder irritability and increasing the functional capacity. Anti-cholinergic drugs such as propantheline or tranquillisers like imipramine on their own tend not to be successful and various surgical procedures have been devised. The most commonly used at present are simple hydrostatic distension, Helmstein distension (Dunn, Smith and Ardran, 1974) or transection of the bladder (Yeates, 1970; Essenhigh and Yeates, 1973; Gibbon *et al.*, 1973). Direct approaches to the nerve supply to the bladder have also been used, by the abdominal route (Marshall, 1954), by the parasacral route (Thiermann, 1953) and by the vaginal route (Ingleman-Sundberg, 1975). Selective sacral neurectomy (Torrens and Griffiths, 1974) using intra-operative cystometry is theoretically attractive, but a procedure on the bladder itself is least liable to affect other organs.

This paper analyses the results of bladder transection in 45 patients with the adult enuretic syndrome treated between 1969 and 1975.

Patients and Procedure

45 patients, 44 with nocturnal enuresis and daytime frequency, urgency or urge incontinence and 1 patient with nocturnal enuresis alone, had bladder transections performed. There were 27 males and 18 females in the series.

The following criteria were used to select the cases with both night and day symptoms

1. Failure to obtain any acceptable response from medical treatment.
2. Absence of any detectable urological abnormality, preferably with a normal bladder capacity under general anaesthesia, and reduced functional capacity when conscious.
3. Diurnal symptoms of frequency and urgency to a degree of inconvenience that made the patients willing to be subjected to what was originally described to them as an experimental major operation.

Procedure

20 patients were found to have what was originally taken endoscopically to be evidence of obstruction to the bladder outlet or urethra. These patients were first treated by urethral dilatation, transurethral resection of the bladder neck or internal urethrotomy. Bladder transection was performed when there was no response to the removal of this apparent outlet obstruction. nine surgeons performed the total of 45 operations, 27 being performed by two of the authors (W. K. Y and D. M. E.).

The technique previously described (Essenhigh and Yeates, 1973) was adhered to by all surgeons.

Results

45 adult patients with the enuretic syndrome operated on by bladder transection were assessed. The results of the operation were graded as follows:

Excellent—no diurnal or nocturnal symptoms.
Very good—minimal diurnal or nocturnal symptoms (*e.g.* mild frequency or nocturnal incontinence not more than once in 2 months).
Good—symptoms improved by approximately 50%.
Improved—symptomatically better than before operation.
Poor—no significant symptomatic improvement.

No patient was made worse by the procedure.

The assessment was based on the patients' last out-patient appointment (20 patients) or from the reply to a questionnaire circulated 1 month prior to this report (25 patients).

Of these 45 patients operated on, 24 patients were asymptomatic (*i.e.* "excellent") or had had a "very good" result at their last review. The fate of the remaining 21 patients are listed in Table I.

Table I

Results of all Bladder Transection Operations and the Outcome of the "Failed" Group of patients.

	Male	Female	Total
Total	27	18	45
Successful operations	16	8	24
Unsuccessful operations	11	10	21
See text for definition			
Outcome of failed group			
Further treatment	5	8	14
Successful further treatment	4	4	8
Failed further treatment	1	4	6
No further treatment	6	2	8
See text for definition			

Table II

Sex and Age Distribution

	Age at operation				
	15-19	20-24	25-29	30-34	35-45
Male	4	5	11	3	4
Female	4	5	7	1	1
Total	8	10	18	4	5

14 patients received further therapy, 8 of whom are now asymptomatic. These were treated by the following methods: 3 had hydrostatic bladder distensions under general anaesthesia, without a balloon catheter, for 3 to 5 min, 2 patients received pituitary snuff at night, 2 patients responded to propantheline and 1 to emepronium bromide. 6 patients failed to respond to further therapy; *viz.* 2 to overdistension of the bladder and 1 to each of the following procedures: Helmstein overdistension as practised by Dunn *et al.*, 1974, repeat bladder transection, imipramine and propantheline. The remaining 7 patients have either been lost to follow-up or are currently undergoing further treatment. 3 patients were lost to follow-up in this group, respectively at 3 months, 6 months and 20 months postoperatively. 2 patients are on the current waiting list for further treatment and 2 patients have relapsed since their last review, having been asymptomatic for 20 months each. 1 patient's symptoms returned after a urinary tract infection, the other patient's symptoms returned after a tubal ligation.

The period of follow-up has varied from a maximum of 77 months to 3 months. All but 8 patients have been followed-up for more than 1 year.

Fig. 1 shows the number of patients followed-up and the number of "successful" ("excellent" or "very good" results) cases at each year of follow-up.

There is no evidence to suggest that the effect of the operation falls off after 6 months.

1. Table II shows the sex/age distribution of the patients operated on and Table III the sex/age distribution of the "successful" operations. A statistically significant difference is found between those patients who had "successful" operations over the age of 25 and those under 25 years of age.
2. Diurnal symptoms are markedly improved by operation. Frequency of micturition occurring hourly or more frequently preoperatively in 26 patients was reduced to 7 patients postoperatively (Fig. 2). Severe urgency of micturition present in 40 patients preoperatively was reduced to 5 patients postoperatively (Fig. 3). Urge incontinence was a debilitating symptom preoperatively in 13 patients; this was reduced to 1 patient postoperatively.
3. Nocturnal incontinence was not quite so effectively cured by bladder transection as the diurnal symptoms, although a marked reduction was found in nearly all cases (Fig. 4).

Complications relating directly to the operation were found in 30 patients out of 45 (Table IV).

Table III

Sex and Age Distribution of Successful Operations

	Age at operation				
	15-19	20-24	25-29	30-34	35-45
Male	3	1	7	2	3
Female	1	1	4	1	1
Total	4	2	11	3	4

Table IV

Early and Late Complications encountered after Bladder Transection

	Total
Early	
Prolonged haematuria beyond 48 hours	8
Suprapubic leakage	10
Wound infection	1
Wound haematoma	1
Urinary tract infection	1
Pneumonia	1
Deaths	0
Late—After discharge from hospital	
Urinary tract infection	6
Renal angle pain and urgency	7
Reflux proved	2
Hesitancy	2
Sexual dysfunction	
Pain on intercourse	2
Loss of libido	1

Discussion

The cystoscopic finding of prominence of the bladder neck may suggest obstruction. However on bimanual examination it is not thickened and it was previously suggested (Yeates, 1973) that this is only a false bladder neck prominence caused by a blow-out of the prostatic urethra below the bladder neck due to oft repeated voluntary external sphincter contraction to prevent urge incontinence. Objective proof of this in females has been provided (Torrens and Collins, 1975). In some cases, however, the bladder neck may be prominent and thickened on bimanual examination (Miller, 1966). These cases may have bladder neck hypertrophy due to bladder neck dysfunction (Turner-Warwick *et al.*, 1973) coincidentally occurring in an enuretic bladder or as part of

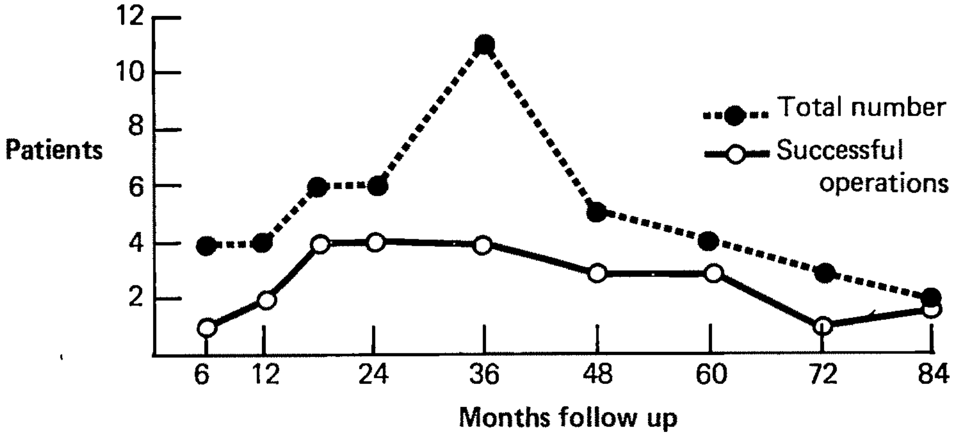

Fig. 1. Follow-up to date indicating the success rate related to the total number of operations.

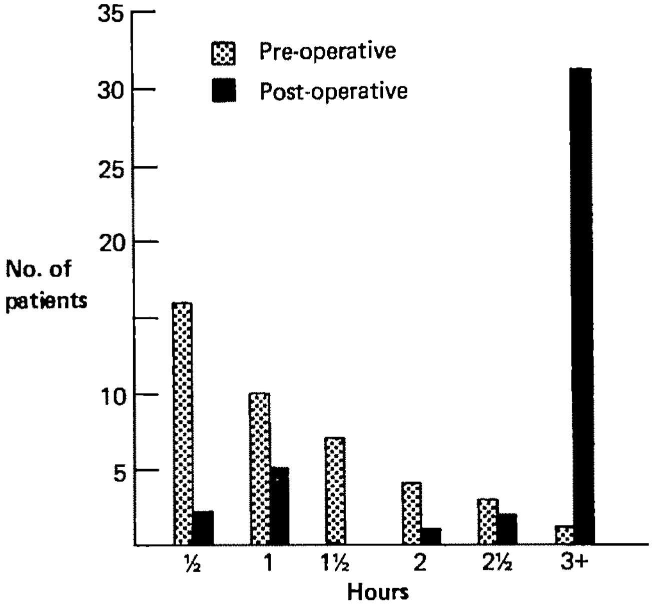

Fig. 2. Preoperative and postoperative incidence of frequency of micturition.

a generalised detrusor thickening. In our group of patients treatment of the supposed outlet obstruction failed in all cases.

The place of cystometry remains uncertain. It is difficult to prove by cystometry whether or not unstable bladders only should be selected for operation although it has been shown postoperatively that the contraction wave is shifted to the right (Gibbon *et al.*, 1973).

Bladder capacities are very difficult to measure by bladder distension. However, if a standard rate of filling at 50 ml/min with a constant temperature of the infusing fluid is performed a comparison between the preoperative and postoperative capacities may be made. The measurement of bladder capacities under anaesthesia at low (10 cm water) pressure indicates the reduction in functional capacity during consciousness or sleep presumably due to neurological instability.

The outlook seems most favourable in cases with the most severe form of the enuretic syndrome

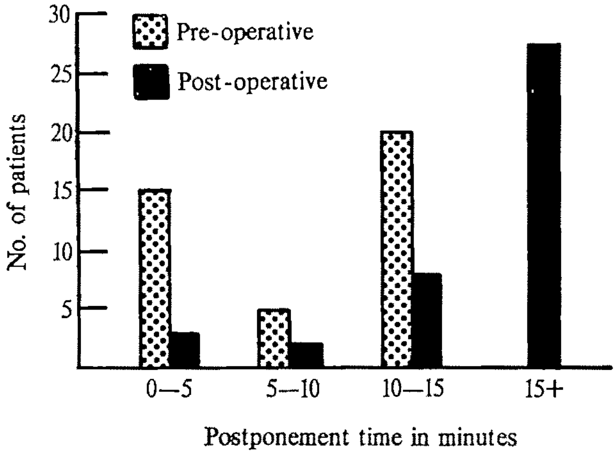

Fig. 3. Preoperative and postoperative incidence of urgency.

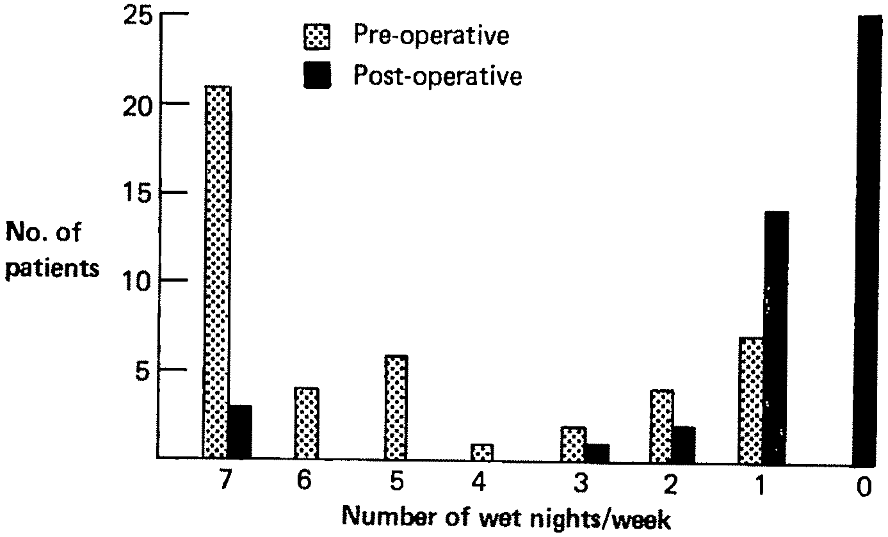

Fig. 4. Preoperative and postoperative incidence of enuresis.

(enuresis, frequency, urgency and urge incontinence), and if the patient is over 25 at the time of operation. The youngest patient operated on in this series was 16 and the operation was successful. Spontaneous cure continues beyond 16 although the rate at which this occurs is difficult to predict as the literature is sparse and its estimates variable (Miller, 1966; Forsythe and Redmond, 1974).

Forsythe and Redmond (1974) found a spontaneous cure rate of 16% in sufferers between 16 and 19 years old. At the age of 20 3% (33 cases) of their total sample were still enuretic. In this series of 33 cases, 3 became dry at 22, 4 at 25 and 5 at 30 years old, giving a spontaneous cure rate of 20% between 20 and 25 and 26 and 30 years old. This rate of spontaneous cure is slow and unpredictable, whereas bladder transection will give a 55% success rate, and 78% overall improvement.

Conclusions

Bladder transection appears to be a valuable operation in cases of primary enuresis, with diurnal symptoms persisting into adult life, who are resistant to medical therapy.

With the exception of those whose symptoms are improving, patients between the ages of 16 and 21 should be seriously considered for bladder transection as the psychological effects of enuresis are particularly severe at this age.

This medium-term follow-up of cases operated on by bladder transection for resistant adult enuresis indicates that the results to date justify the procedure after other methods of treatment have been tried and found to be unsuccessful.

The criteria for operation would seem to be: 1. Patients over the age of 16.
2. Typical severe diurnal and nocturnal enuresis resistant to all previous forms of therapy.
3. Bladder capacity greater than 400 mls under general anaesthesia.

Summary

45 patients with adult enuresis have been treated by bladder transection between 1969 and 1975 and followed-up from 6 months to 7 years.

24 patients are now asymptomatic.

Bladder transection gave very worthwhile results in 53% of cases.

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The Authors

J. R. Hindmarsh, FRCS, FRCSE, Research Fellow, Northern Counties Kidney Research Fund.
D. M. Essenhigh, MCh, FRCS, Consultant Urologist, Newcastle University Hospitals.
W. Keith Yeates, MD, MS, FRCS, Consultant Urologist, Newcastle University Hospitals.

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Short Case Report

Urethral Injury following Use of a Thomas Splint

A 24-year-old male sustained bilateral femoral shaft fractures in a car accident. These were treated conservatively by skeletal traction using Thomas splints. He developed acute retention shortly after admission and was catheterised. 3 weeks later he was noted to be leaking urine from his perineum. On removing the splint he was found to have eroded away the floor of his urethra at the base of the scrotum (Fig. 1). As the roof of the urethra was intact it was decided to treat this conservatively and a suprapubic catheter was therefore inserted. Healing of the perineal wound initially occurred rapidly and final healing was complete after 23 weeks (Fig. 2). At the present time he requires monthly urethral bouginage and it is likely that (after 12 months) he will require a urethroplasty.

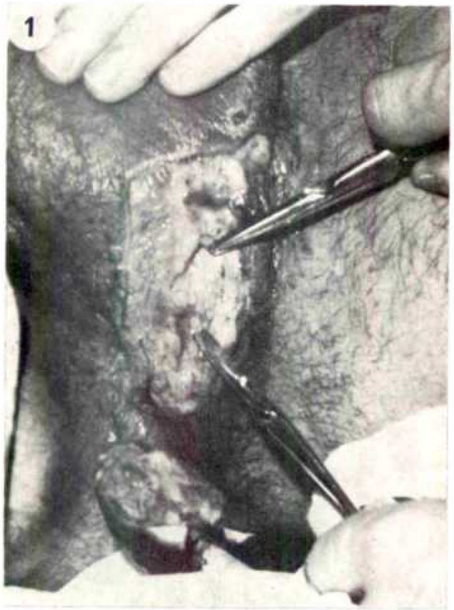

Fig. 1. The perineum on removing the splint, the forceps show the ends of the urethra.

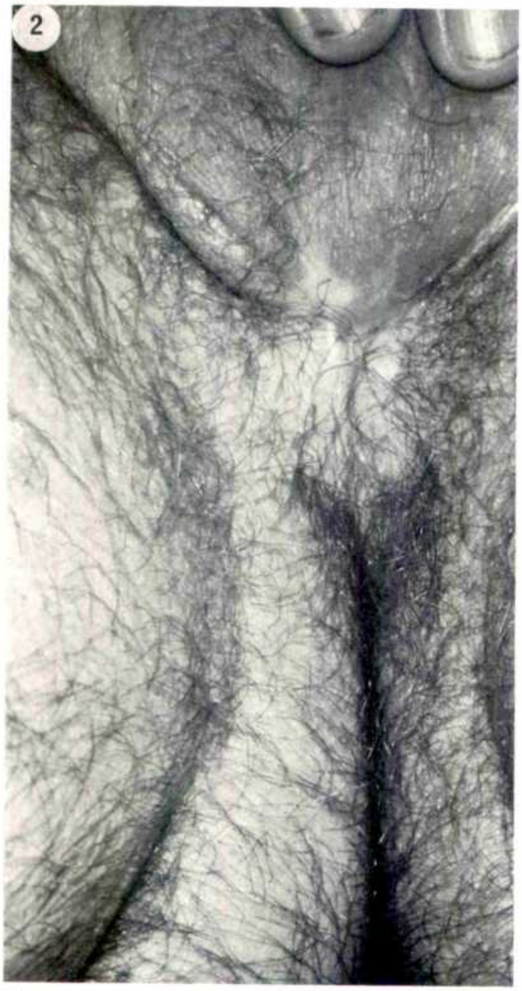

Fig. 2. The perineum, healed at 161 days.

Comment

The urethral injury in this case was caused by the urethra being trapped between a catheter and the ring of the Thomas splint. In view of the presence of infected dead tissue the formation of a stricture was inevitable. Mitchell (1971) believes that some degree of stricture formation always follows anterior urethral injuries.

J. R. C Logie and W. H. H. Garvie
Aberdeen Royal Infirmary, Aberdeen, Scotland

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Intermittent Catheterisation in Congenital Neurogenic Bladder: A Preliminary Report

K. LIGHT and P. J. P. VAN BLERK
Division of Urology, University of the Witwatersrand Medical School; and The Transvaal Memorial Hospital for Children, Johannesburg

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Intermittent catheterisation is now a well-recognised method of treatment in the management of patients with neurogenic bladder disorders. There is still some constroversy as to whether this should be sterile or not (Guttmann and Frankel, 1966; Comarr, 1972; Lapides *et al.*, 1972). We previously reported our unfavourable results of urinary diversion in congenital neurogenic bladders (Light, Cohen and Van Blerk, 1977) and felt justified in applying intermittent catheterisation as a possible alternative. This paper summarises the preliminary experience and results of using clean intermittent catheterisation in patients attending a Spinal Defects Clinic.

Patients and Method

Clean intermittent catheterisation was started in March 1975 and 55 patients are currently so managed. The youngest is a male of 7 months and the oldest a 17-year-old female. The sex and age distribution is shown in Table I. The diagnosis was myelomeningocoele in 48, sacral agenesis in 4 and paraplegia in 3.

The method of catheterisation is similar to the routine advocated by Lapides *et al.* (1972). The size of catheter varies from an 8 to 16 F depending on the age and sex of the child. The catheterisation is performed at 3-hourly intervals with children less than 5 years of age and 4-hourly in older children, a clean catheter being used daily. After use the catheter is rinsed through with tap water and kept in a dry container. Fluids are restricted for 2 hours preceding the final evening catheterisation which is usually at 10 p.m. Catheterisation is not performed during the night and lubrication is used only in male patients. Catheterisation is performed by the parents or non-medical personnel of schools or residential centres. 6 male and 4 female patients aged 6 to 16 years do self-catheterisation. No patient has been managed in hospital. The dangers of haphazard catheterisation are carefully explained. Initially the type of neurogenic bladder was not categorised. More

Table I

Age and Sex Distribution of 55 Patients

Age (years)	0-2	3-6	7-10	11-17	Total
Sex: Male	2	7	6	5	20
Female	7	11	10	7	35

Table II

Reasons for Failure

1. Low urethral pressure profile	7
2. Presence of urethral sensation	2
3. Small bladder capacity	2
4. Urethral stricture	1
5. Unco-operative	2
Total	14

recently this has been attempted with cystometry and urethral pressure profile recordings on a CO_2 cystometer and these results will be reported separately. Probanthene, an anti-cholinergic, was used for the hyper-reflexic bladders and ephedrine hydrochloride, an alpha stimulator, for those with a low urethral pressure profile. The main indications for intermittent catheterisation were incontinence in 33, upper tract deterioration in 16 and persistent urinary infections in 6 patients.

Excretory urography was performed at 3 months and then 6 months in those patients with deteriorating upper tracts and at 6-monthly intervals in those with normal upper tracts. Continuous catheter-drainage was used in selected cases prior to starting intermittent catheterisation.

The follow-up period is from 6 to 18 months.

Results

(a) Continence

This was defined as: excellent—if patient dry for 24 hours; good—dry during the day, damp overnight; improved—drier than before intermittent catheterisation; failed—no response at all. 46 patients have been followed for a minimum of 6 months. 17 patients (37%) showed excellent continence, 14 (30%) showed good continence and 1 patient improved in the degree of continence. 14 patients (30·4%) were regarded as failures and the commonest reason was a low urethral pressure profile (Table II). The type of bladder, *i.e.* hyper- or a-reflexia, showed no correlation with the degree of incontinence provided that Probanthene was used with hyper-reflexia.

(b) Upper Tracts

The upper tracts were assessed on excretory urography at 6 months and 1 year after starting intermittent catheterisation (Table III). The patients at 1 year were not included in the 6-monthly analysis.

6 patients with initial deterioration in the upper tracts and 3 with normal upper tracts have not been followed for 6 months as yet, leaving 46 for further analysis. It can be seen that no upper tract deteriorated and, in fact, 10 patients with deteriorating upper tracts showed marked radiological improvement, while 36 patients remained normal.

(c) Urinary Tract Infection

Isolated urinary tract infection has been defined as one specimen with $>10^5$ organisms during a 6-month period, while recurrent urinary tract infection has 2 or more infections in 6 months. The incidence of urinary tract infection while on intermittent catheterisation is shown in Table IV. 40 patients were available for analysis: 21 (52·5%) patients are currently maintaining sterile urine, while only 11 (27·5%) experienced recurrent infections. In all patients who developed a

Table III

Status of the Upper Tracts

	Follow-up at 6 months	Follow-up at 12 months
Remained normal	12	20
Improved	3	7
Remained static	—	4
Deteriorated	0	0
Total patient No.	15	31

Table IV

Urinary Infection and Intermittent Catheterisation

	Patient No.	Per cent
Sterile on antibiotics	7	17·5
No antibiotics	14	35
Infected: Isolated	8	20
Recurrent	11	27·5
Total	40	

symptomatic infection, misuse of the catheter was found to be present, either on the part of the patients or hospital staff. On intermittent catheterisation there was a marked improvement or total disappearance in the incidence of urinary infection.

Discussion

Intermittent catheterisation was first described by Guttmann and Frankel (1966). It is only since the report by Lapides *et al* (1972), however, that this procedure has become more widely adopted and the emphasis is now on regular, clean catheterisation as opposed to sterile catheterisation advocated by Guttmann and Frankel (1966) and Comarr (1972).

The follow-up period in the present report is short, but it has shown that the patient should persist with intermittent catheterisation. The three main problems of incontinence, urinary tract infection and upper tract deterioration have been either improved or controlled. Furthermore, there are 10 cases which showed marked improvement in the upper tracts after this type of management was instituted. These cases would previously have been subjected to urinary diversion. This has been avoided, at least temporarily, by this method of treatment. 16 patients have had urinary diversion deferred for upper tract deterioration and these patients almost invariably had significant reflux which has been shown to be the most important factor causing upper tract deterioration (Light and van Blerk, 1977). At present, if a patient is found on follow-up to have significant reflux or obstructed hydro-ureter, intermittent catheterisation is started immediately. This has been shown to occur within the first 4 years of life, which explains the number of patients in this age-group in the series (Light and van Blerk, 1976). Lyon, Scott and Marshall (1975) have also strongly advocated this form of treatment instead of diversion in these patients.

If the patient maintains normal upper and lower tracts, intermittent catheterisation for incontinence is started at the age of 4 years. The majority of patients require either an anticholinergic or an alpha stimulator drug in addition to the catheter in order to improve continence. Marked improvement in continence was found in 67·4% of patients and, more important, the uriniferous odour was removed and social rehabilitation was made possible.

The incidence of patients with sterile urine was 52·5%, comparable to the 48% quoted by Lapides *et al.* (1976). There appears to be a relationship between the state of the bladder and those patients with recurrent infection, in that infection occurred more commonly when gross trabeculation and/or sacculation was present. The control of infections is important, especially in those patients with hyper-reflexic bladders, as this still further decreases the functional bladder capacity by promoting uninhibited contractions and so aggravating the urinary incontinence.

No case of traumatic urethritis has been observed even in the youngest male patient of 7 months. The 1 urethral stricture was present prior to commencing catheterisation.

The majority of parents and patients express preference for the intermittent catheterisation to that of the Crédé manoeuvre.

As a result of this preliminary experience with intermittent catheterisation, we have now relegated urinary diversion to the last resort in treating this type of patient.

Summary

53 children with congenital neurogenic bladders are currently managed on intermittent catheterisation.

The problems of continence, urinary tract infection and upper tract deterioration have to date been controlled reasonably successfully and the need for urinary diversion appears to have been obviated.

Complications have been negligible and parents and patients alike prefer this method to the Crédé manoeuvre.

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The Authors

K. Light, FCS(SA), Consultant Urological Surgeon and Lecturer.
P. J. P. van Blerk, DipSurg, Professor of Urology.

Requests for reprints to Department of Urology, University of the Witwatersrand Medical School, Johannesburg, Republic of South Africa.

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Endoscopic Removal of Bladder Stones in Adults

S. S. BAPAT
Bapat Hospital, Pune, India

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One important inherent defect in the older instruments is that they have no visual aid; the crushing process necessarily is a blind process. This leads to two major possible complications, *viz.* incomplete crushing and removal of fragments and damage to the bladder wall.

We now have better optics, mechanics and electronics, so that we can crush large bladder calculi completely under visual control and confirm total evacuation of the fragments, thus assuring safety.

Practice and Procedures

The present paper is based on the personal experience of removal of vesical calculi of all sizes in 100 adult patients whose urethras would accept the adult 23 Ch. panendoscope.

Three procedures were used for removal of the vesical calculi in these 100 patients: (1) Extraction by Dormia basket, (2) Cystoscopic lithotripsy and (3) Electronic lithotripsy with Russian-made "URAT 1" lithotriptor.

These 100 patients were treated either at the Sassoon General Hospitals, Pune, or at a private Urological Clinic in Pune, since 1970. Their age and sex distribution is shown in Tables I and II.

All patients had their haemogram, blood urea and sugar estimated and had their urinalysis done. Abdomen was X-rayed in all cases which showed renal calculi in addition to the vesical calculi, in 11 cases. Those cases who had urinary infection were first treated by appropriate drugs and then taken up for crushing.

Size of Stones

It varied greatly from about 1 cm diameter to 7·5 cm in maximum diameter. A single stone was present in 82 cases and the remaining had more than 1 stone. 1 patient had numerous soft phosphatic stones in the bladder which could not be counted due to overlapping. The majority of the stones were of the mixed type. Those which were pure oxalate stones were indeed quite hard to crush.

Table I

Age Distribution

Age-group (years)	No. of cases
14 to 20	5
21 to 30	19
31 to 40	24
41 to 50	25
51 to 60	15
61 to 70	12

The youngest patient was 14 years old and the oldest 70 years old.

Table II

Sex Distribution

Sex	No. of cases
Males	95
Females	5

Instruments Used

1. "Hopkins" Storz panendo-cystoscope, with fibre light transmission, sizes of sheaths were 17 and 23 Ch.
2. Hopkins Storz cystoscopic lithotrite.
3. "Dormia basket" stone dislodger.
4. "URAT 1", electronic stone crusher (made in USSR).
5. Ellick's evacuator.
6. Storz—endoscopic photographic equipment.
7. Neoplex plastic filiform guides and followers—(Urethral dilators).
8. Storz, trans-urethral resectoscope 24 Ch.

Selection of the Type of Procedure Employed

This was mainly determined by the size of the stone or stones. Smaller stones which were held up in the bladder or prostatic urethra and whose diameter did not exceed 1·25 cm were successfully removed by the Dormia basket. For this a smaller sheath (17 Ch.) was routinely used. The size of the stone was measured *in situ* within the bladder with the help of the markings on the Dormia basket plastic covering sheath. For the removal of stones which were little more than 1 cm in diameter urethral dilatation was done up to 30 Ch., with plastic bougies. 43 patients were treated by this method. (This does not include cases where the stones were extracted from the ureter with the help of the Dormia basket.)

Those cases where the stones were between 1·25 to 2·5 cm in maximum diameter, a cystoscopic lithotrite was used to crush the stones and then the fragments were extracted with the help of the Ellick's evacuator. 19 patients were treated by this method.

Stones bigger than 2·5 cm were crushed with the help of the Russian-made electronic lithotriptor "URAT 1". This is the latest in the line of the lithotrites and uses the principal of capacitor discharge (Wallace, Cole and Davies, 1972). This electric discharge of 400 amps and 1,500 volts is generated in the form of a pulse-beat lasting for one microsecond. Hence it does no harm. This powerful electric discharge is conducted through a specially made bipolar electrode whose outer diameter is 10 Ch. Hence it is essential to use an adult operating panendoscope. After passing the panendoscope in to the bladder about 150 to 175 ml of irrigating fluid is introduced. Under visual control, the electrode is introduced into the bladder and advanced towards the most prominent convex surface of the stone. Care is taken to see that the tip of the probe does not touch the stone and is kept about ½ to 1 centimetre away. With the help of the foot switch the machine is activated for short periods, not exceeding 1 or 2 seconds, at a time. Each burst makes a shrill noise and creates strong waves within the fluid medium in the bladder. These waves hit the hard surface of the stone, crack it and the cortical layer of the stone breaks off. Firing is continued on the hardness of the stone, the stone breaks into 2 or more major fragments. Once this is done, further crushing is quite easy. Subsequent firing is done on the freshly exposed inner surface of the fragment, which very easily breaks. When the stone fragments are small enough they are evacuated by Ellick's evacuator. Smaller fragments, smaller than the tip of the electrode, were not crushed. In case accidentally the direction of the fire on the smaller fragments missed, the mucosa of the bladder does not suffer any damage other than mild eccimosis. This is due to the elasticity of the bladder wall in contrast to the hard surface of the stone. 38 cases were treated by this technique (Table III).

Table III

Types of Procedures

Types of procedure done	No. of cases
Dormia basket extraction of bladder stones	43
Cystoscopic lithotrity	19
Electronic lithotripsy with "URAT 1"	38

Associated Obstructive Conditions and their Management

Association of bladder stones with bladder outlet obstruction is a very common finding. In the present series of 100 cases, 40 cases had bladder outlet obstruction of varying degrees. Of these 40 cases, 32 cases had bladder-neck obstruction due to hyperplasia of the periurethral glands of the prostate, who mostly belonged to the older age-group. 8 patients had stricture of urethra.

Of the 32 patients who belonged to the bladder-neck obstruction group due to enlargement of the prostate gland, 18 underwent immediate transurethral resection of the prostate gland (T.U.R.) under the same anaesthesia. 8 patients underwent staged T.U.R. after 4 to 6 days. Decision as to whether to do immediate T.U.R. or a staged T.U.R. was taken on the size of the stone and thereby time taken to crush and evacuate the fragments. In all the above cases the stones were crushed and removed first, followed by T.U.R. of prostate.

14 patients in this enlarged prostate group preferred not to have immediate or staged T.U.R. After removal of the stones they seemed to be happy and comfortable. Removal of the stone helped to reduce the irritative cystitis and trigonitis with reduction of mucosal oedema at the bladder neck, and thereby widening the bladder outlet a little. Some of these patients have been followed up to 4 years and they seem to be comfortable.

8 patients had stricture of urethra in the bulbomembranous area. Of these two were post-prostatectomy strictures. All these cases were dilated under visual control with the help of filiform bougies and followers. This was followed by extraction or crushing and evacuation of the stones. All these patients are responding satisfactorily to periodic dilatations.

Complications and Postoperative Stay

In the first group of basket extraction of the stones the patients were discharged on the same day after about 6 to 8 hours. Slight burning on micturition was all that was complained of by these patients.

In the other two groups of cystoscopic and electronic lithotripsy, where the fragments had to be evacuated by the Ellick's evacuator due to sudden distention and collapse of the bladder, slight haematuria was noticed. This haematuria was noted for 1 to 3 days and was of no significance. Burning micturition was also noted. In spite of the instrumentation, patients were much more comfortable than before operation. Hospital stay varied from 2 to 4 days.

Patients who underwent immediate or staged T.U.R. had a correspondingly longer hospital stay.

Apart from the above, no other serious complications were noted. There was no mortality.

Discussion

73% of the patients were below 50 years of age as compared to 14% in the same age-group as reported by Rouvalis (1970) in his series, and 25% as reported by Angeloff (1972). Most of the patients who belonged to this age-group belonged to the low-income group. It is common knowledge that primary bladder stones are common in under-nourished persons. Similar high incidence of primary vesical calculi was also seen in the now affluent countries in the past. It is for this younger age-group of patients that this procedure of endoscopic removal of the calculi has proved a great boon. They can return to heavy manual labour within a matter of a few days. This is not at all possible if these stones are removed by open cystolithotomy. Previous surgery on the bladder, neurogenic bladder, prostatic enlargement, size and hardness of stone or stricture of the urethra are no longer contra-indications for this type of surgery. In those cases where there is a big median lobe of the prostate and the stones are lodged in this retroprostatic pouch, technically it becomes difficult to approach the stone properly and crush it. Hence in such cases it is advisable to resect the prostate first and then tackle the stone. This could be done either at the same sitting or as a staged procedure depending upon the time taken for T.U.R. and the size and hardness of the stone. In the present series, stones were removed first followed by T.U.R.

This procedure of endoscopic removal of bladder stones is a safe procedure provided the operator has the appropriate instruments and the appropriate skill.

Summary

Endoscopic removal of bladder stones of all sizes in adults has been discussed and illustrated by 100 cases. 3 different techniques were used to remove the stones *viz.* (1) extraction by Dormia basket, (2) cystoscopic lithotrity and (3) electronic lithotripsy by Russian-made "URAT 1".

Safety and economic advantages to the patients have been discussed.

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The Author

S. S. Bapat, MS, FRCS, FRCSE, Consultant Urologist.

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Recording of Vesical Voiding Pressure by Means of CO_2-perfusion

R. TSCHOLL and A. LENZIN
Urological Clinic of the University of Bern, Switzerland

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Bladder pressure during micturition is one of the basic urodynamic parameters (Claridge, 1966; Smith, 1968). For assessing the function of the lower urinary tract it is as important as the vesical pressure during filling.

The bladder's response to filling can easily be evaluated by air-cystometry (Merrill, Bradley and Markland, 1971). The voiding pressure should be measurable in an equally simple way. No additional manoeuvre should be necessary, such as connecting the catheter to some other machinery or introducing another type of catheter into the bladder.

An attempt was made to simplify the urodynamic investigation of the lower urinary tract by recording the vesical pressure during micturition with an air-cystometer and by using a catheter which would also be suitable for cystometry and urethral pressure profile.

In a preliminary experiment (Fig. 1) a urethral catheter (F5) was placed into the full urinary bladder of an individual not suffering from bladder disease. The catheter was connected to an air-cystometer. By introducing CO_2 through the catheter into the bladder while the subject was

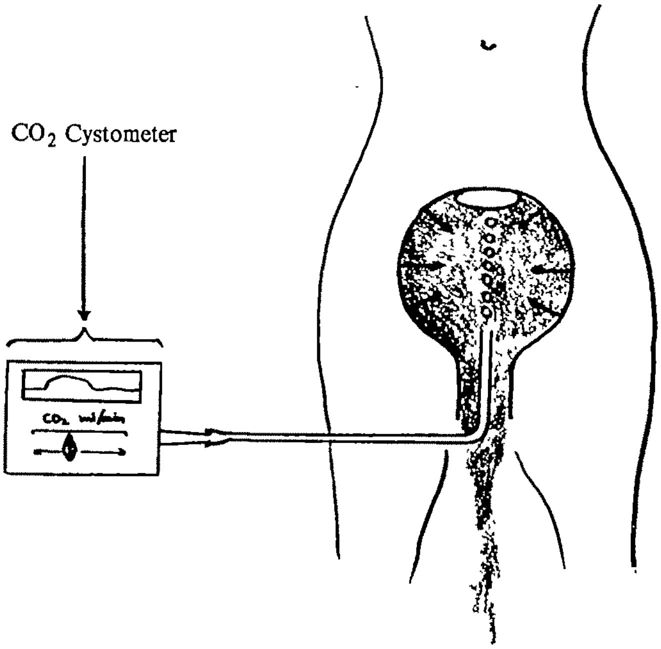

Fig. 1.

urinating around the catheter a reproducible pressure curve could be recorded by the CO_2-cystometer.

Two questions, however, have to be answered:

1. How do the values thus found correlate with those measured by conventional liquid transmission to a pressure transducer?
2. How does the CO_2-perfusion influence the intravesical voiding pressure if at all?

Method

2 catheters (F5) were introduced into the bladder of 10 healthy women (Fig. 2). One catheter (*a* in Fig. 2) was connected to a pressure transducer (Statham P23Db), the other (*b* in Fig. 2) to an air-cystometer (DISA).

In answer to question 1: Each woman had to empty her bladder three times. During micturition CO_2 was flowing into the bladder at a rate of 100 ml/min through the catheter (*b*) connected to the CO_2-cystometer. The voiding pressure was recorded simultaneously by means of liquid transmission and of gas-perfusion. The correlation of the pressure values thus measured in 2 different ways was then computed.

In answer to question 2: The voiding pressures of 3 women were measured 4 times with the conventional chain while there was no CO_2-perfusion. The micturitions and the measurements were then repeated in the same way but with CO_2 being introduced into the bladder at rates of 25, 50, 100 and 200 ml/min. The mean values of the pressures recorded, with and without gas perfusion, were compared and analysed with the *t*-test.

Results

1. The peak pressure values measured by liquid transmission to a transducer and those recorded by CO_2-perfusion correlate quite sufficiently, the correlation coefficient amounting to 0·9847 (Fig. 3).

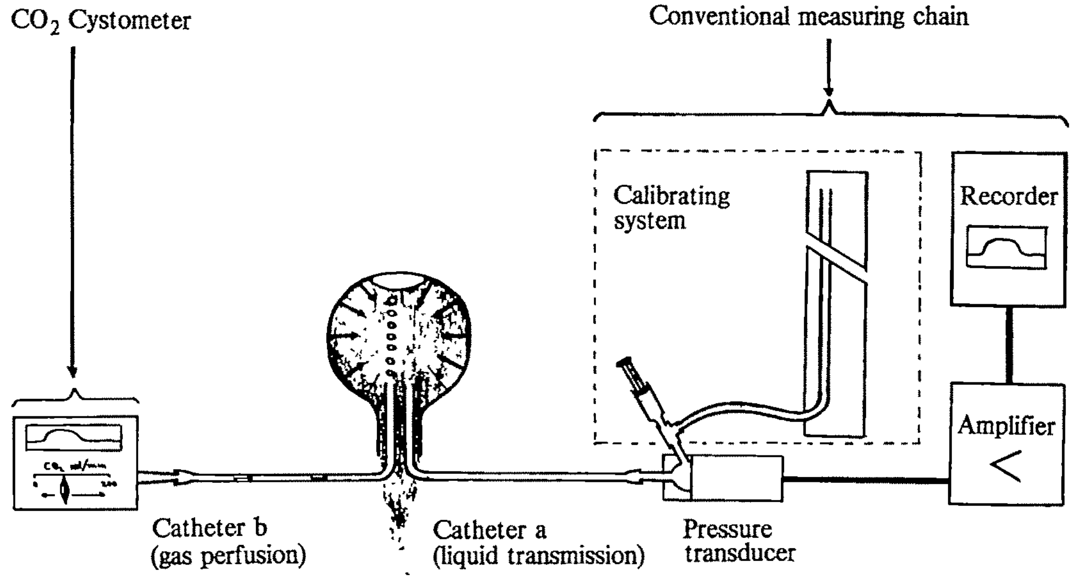
CO2 Cystometer
Conventional measuring chain
Calibrating system
Recorder
Amplifier
CO2 ml/min
0
200
Catheter b (gas perfusion)
Catheter a (liquid transmission)
Pressure transducer

Fig. 2.

For 1 micturition not only the peak pressure but the shape of the curves recorded by the two procedures agree very well (Fig. 4).

2. CO_2-perfusion at rates between 25 and 200 ml/min does not influence the voiding pressure, as is illustrated by the recording of one of these women. The curves without CO_2-perfusion hardly differ from the one recorded under CO_2-perfusion (Fig. 5).

The statistical analysis confirms that there is no significant difference between the values found while there is no CO_2-perfusion and those recorded while CO_2 is flowing into the contracting bladder (Fig. 6).

Discussion

The vesical pressure during micturition can be accurately recorded by CO_2-perfusion. The same equipment is used as for air-cystometry. Therefore, the measurement of the vesical voiding pressure can be built into a procedure for urodynamic evaluation of the lower urinary tract which will supply all clinically relevant data (vesical voiding pressure, urinary flow rate, urine volume, cystometry graph and urethral pressure profile) within 5 to 10 min. It can be executed by someone without special training as once initiated it is practically a simple procedure.

The whole investigation is relatively inexpensive and simple enough to be used in urological practice. It is an efficient screening method before referring a patient to a more sophisticated urodynamic unit.

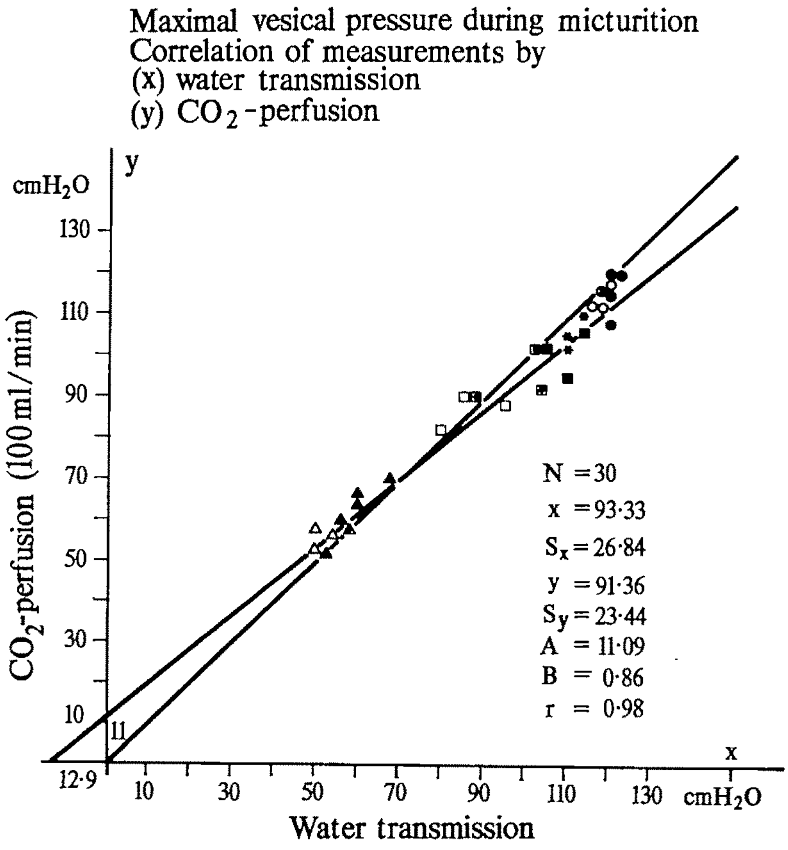

Fig. 3.

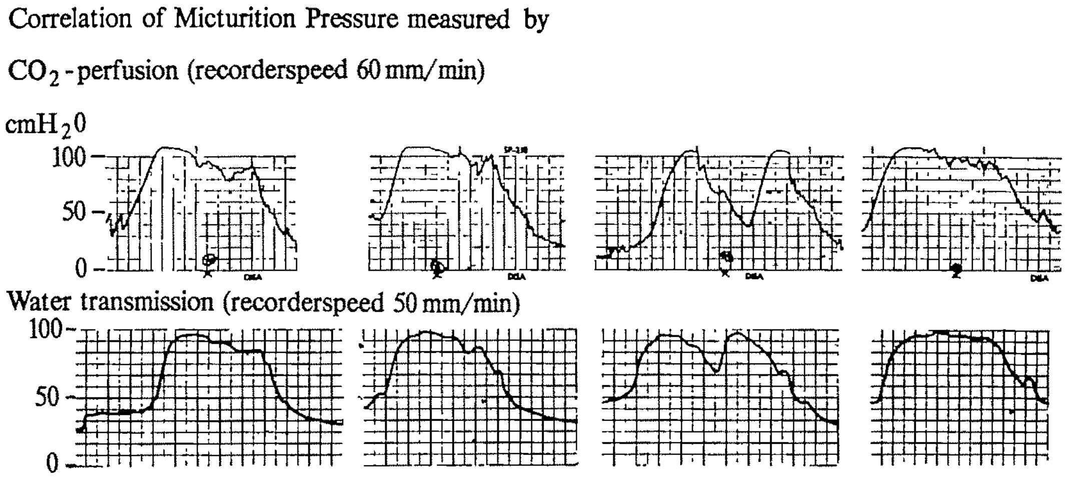

Fig. 4.

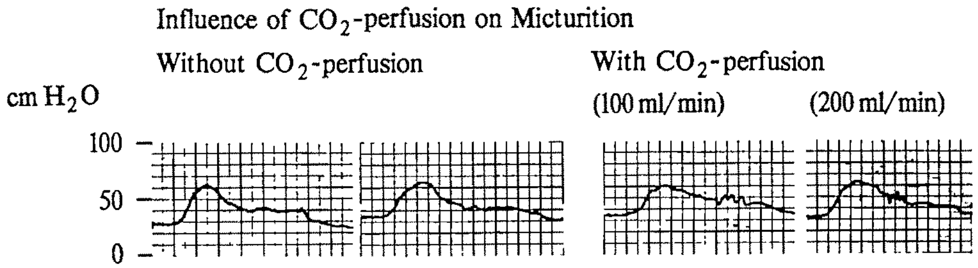

Fig. 5.

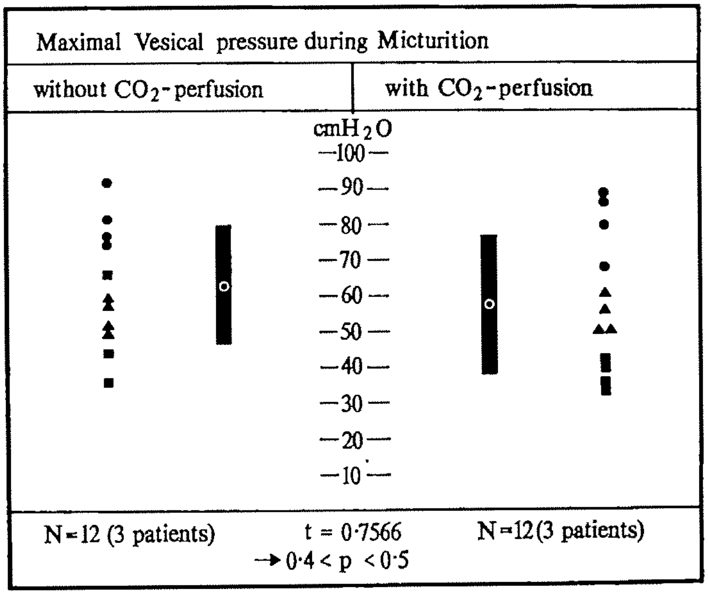

Fig. 6.

Summary

By means of a CO_2-cystometer, carbon dioxide is introduced through a urethral catheter (F5) into the full urinary bladder while the subject is urinating around the catheter. A reproducible pressure curve can be recorded.

The pressure values measured by CO_2-perfusion correlate very well with those measured simultaneously by a conventional fluid method. It can be statistically demonstrated that the CO_2 flowing into the bladder does not influence the vesical voiding pressure. It is concluded that the vesical pressure during micturition can be accurately recorded by CO_2-perfusion.

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The Authors

R. Tscholl, MD.
A. Lenzin, MD.

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Short Case Report

Wilms Tumour with Left Cord Metastasis

A 9-month-old male child was admitted for a mass in the left half of the abdomen. The mass was globular, non-tender, firm and 4″ × 3″ in size. The child was blind since birth with no history of infection and had bilateral complete corneal opacity, buphthalmos, staphyloma, xerosis and complete loss of vision. Possibility of congenital aniridia could not be ruled out (Fig. 1). X-ray of the abdomen revealed a large soft tissue shadow. Intravenous pyelography showed a normal right kidney and a small amount of dye in the lower left calyces with downward displacement of the collecting system. Chest X-ray was normal. At operation the tumour was encapsulated, and there were no tumour thrombi in the left renal vein or inferior vena cava. Lymph nodes were not enlarged. Left nephrectomy was performed and histopathology confirmed the diagnosis of nephroblastoma.

The patient reported 3 months later with a left inguinoscrotal firm, non-tender swelling (Fig. 2). chest X-ray was normal. High ligation of the cord and orchidectomy was performed. Microscopically the mass was metastatic nephroblastoma, the left testis was normal. 1½ years later, the child is healthy and free of recurrence.

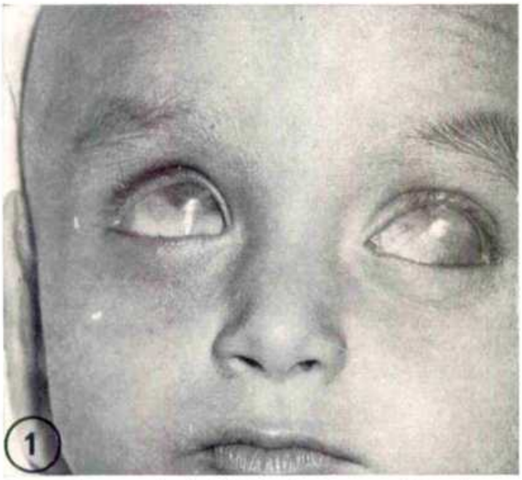

Fig. 1. Photograph of child showing abnormalities of eyes.

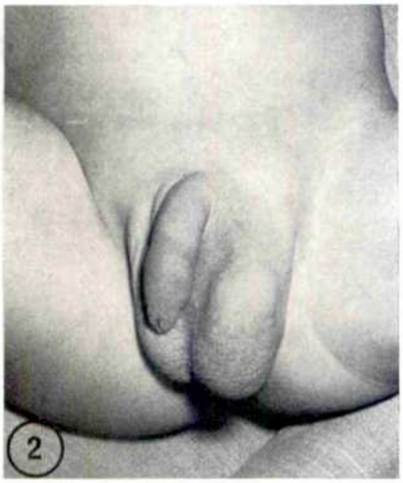

Fig. 2. Inguino-scrotal swelling—metastatic mass.

Comment

The development of a metastatic deposit in the spermatic cord in this case suggests that such a spread can occur without direct involvement of the spermatic vein. Dew (1928) reported a similar case.

KRISHNA YADAV and I. C. PATHAK
Department of Paediatric Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India

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Effect of Phentolamine on Perineal Muscle EMG Activity in Paraplegia

JOHN B. NANNINGA, PAUL KAPLAN and S. LAL

Department of Urology, Northwestern University Medical School and the Rehabilitation Institute of Chicago, Chicago, Illinois 60611, USA

(Received 18 November 1976; accepted for publication 17 January 1977)

There has been increasing evidence that the region of the external sphincter is under some degree of adrenergic control, in addition to the generally accepted concept of somatic motor innervation (Donker, Ivanovici and Noach, 1972; Elbadawi and Schenk, 1974; Ghoneim *et al.*, 1975). The question of whether the adrenergic influence is exerted on smooth or striated muscle, or both, is as yet not resolved.

We recently made an observation which might shed light on this problem. During routine cystometry and perineal muscle electromyography (EMG) on a paraplegic patient, the patient exhibited autonomic hyperreflexia (headache, flushing of the skin and hypertension). The alpha-adrenergic blocking agent, phentolamine (Regitine, Ciba), was administered intravenously to reduce the blood pressure. Shortly thereafter, a decrease in perineal muscle EMG activity was noted even though the bladder had not been drained and bladder pressure remained elevated. Therefore, during subsequent cystometry and perineal EMG evaluation of three other patients, particular attention was directed at the EMG activity when phentolamine was administered for autonomic hyperreflexia.

Materials and Methods

3 paraplegic patients (levels C_6, C_7, T_4) underwent cystometry and perineal EMG.

The cystometrograms were performed by infusing sterile saline solution into the bladder via a 18 F catheter at a rate of about 1 ml/sec. Bladder pressure was measured on an electronic recording machine.

The perineal muscle activity was recorded via monopolar needle electrodes inserted through the perineum into the area lateral and just distal to the apex of the prostate, where the external sphincter is located. Insertional activity was monitored by oscilloscope. In 2 patients, fast sweep measurement (10 milliseconds/centimetre) was measured on a TECA TE4 electromyograph and recorded on tape. Analysis was made from the recordings, determining the mean frequency and amplitude of the spikes. In the third patient, the EMG activity was recorded on a direct write-out recorder (Hewlett-Packard, 7754) at a speed of 2 mm/sec.

As the bladder was filled, EMG activity was recorded simultaneously. Blood pressure was measured periodically as the bladder was filled. When the micturition reflex occurred, as evidenced by a rise in bladder pressure, the blood pressure was taken. As the patient developed signs of autonomic hyperreflexia, phentolamine was administered intravenously (10 mg). Bladder volume was maintained at a constant level to maintain bladder pressure. Small increments of fluid were added to the bladder when urine leaked around the catheter.

The recording was continued during the period in which the blood pressure returned to normal, following administration of the phentolamine. This was in the order of 3-5 minutes. The bladder was then drained by gravity.

Following the drainage of the bladder, the urethral pressure profile was measured by infusion of fluid into the urethra at a rate of 2 ml/min, monitoring the pressure in the catheter and withdrawing the catheter slowly by hand (Brown and Wickham, 1969). These values were compared with urethral pressure measured prior to this study.

Results

These patients all demonstrated an increase in perineal EMG activity as the bladder filled, particularly as the bladder pressure rose and the micturition reflex occurred. This dyssynergy between bladder and external sphincter is frequently noted in patients with spinal injury, as were these patients. Following the injection of phentolamine, the EMG activity was noted to fall. This occurred even though the bladder pressure remained elevated (Fig. 1). From the table, it is noted that blood pressure fell promptly following the phentolamine injection. There was a fall in urethral pressure demonstrated, although the decrease might have been greater if the measurements had been done witin a minute or two after the phentolamine injection.

The effect was followed for about 5 minutes, at which point the bladder was completely drained and the EMG activity might be expected to subside spontaneously.

Interpretation

Huggins, Walker and Noonan (1939) observed that sympathetic nerves somehow influenced the striated muscle surrounding the urethra. They found that sectioning the presacral nerves improved bladder emptying in certain patients. More recently, Petersen, Kollberg and Dhuner (1961) noted that the external sphincter demonstrated marked resistance to intravenously administered succinylcholine, as evidenced by EMG activity. Abel *et al.* (1974) reported the effect of phentolamine in decreasing sphincter pressure in 2 paraplegic patients. They believed that the effect was on the smooth muscle in the urethra, however. We believe that the electrical activity recorded in our study was definitely from striated muscle because of the position of electrodes and the typical wave form of striated muscle.

There are various mechanisms by which sympathomimetic amines may exert their effect on skeletal muscle (Bowman and Nott, 1969). Adrenaline and noradrenaline would appear to

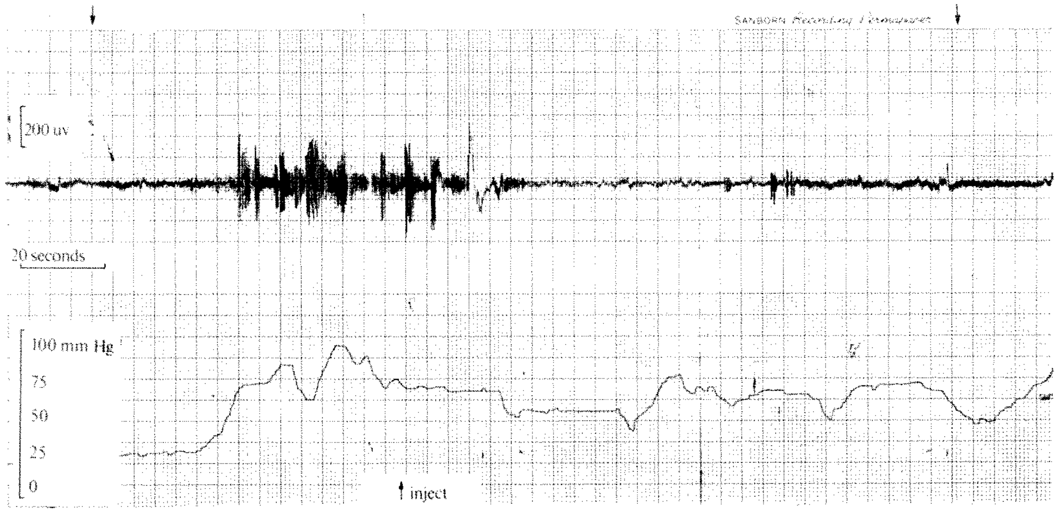

Fig. 1. The top tracing is the EMG and bottom tracing the bladder pressure. The arrow marks the point at which phentolamine 10 mg was injected intravenously. The decrease in EMG activity is evident.

Table I

Effect of Phentolamine on Bladder and EMG

Patient	Blood pressure	Bladder pressure	EMG amplitude	Spikes/sec.	Sphincter pressure
1. Before injection	130/90	130 mm Hg	730 μV ± 83	8·7 ± 2	96 mm Hg
After injection	118/60	120 mm Hg	355 μV ± 12	5·8 ± 2	80 mm Hg
2. Before injection	220/130	150 mm Hg	490 μV ± 30	8·6 ± 5	140 mm Hg
After injection	140/80	150 mm Hg	250 μV ± 8	4·6 ± 2	110 mm Hg

facilitate neuromuscular transmission and may exert an effect on the external sphincter. Thus, there may be part of normal sphincter activity, possibly the resting tension and the rise in resistance during bladder filling, which is under sympathetic control. In patients with spinal cord defects, the effect of the adrenergic system may be accentuated, thus producing the exaggerated effect in the external sphincter. It is conceivable that the inhibition in sphincter activity demonstrated in our study by the alpha-blocking agent may explain the mechanism by which normal relaxation of the external sphincter occurs during micturition. That is, by a decrease in sympathetic activity, urine can pass through the urethra during a bladder contraction.

The findings in this study do not negate the traditional view that somatic motor fibres are contained in the nerves to the external sphincter. Voluntary contraction of this muscle is an obvious function. But the data presented here seem to us to substantiate further the concept that there is an adrenergic component to external sphincter function which would seem related to the straited muscle of the sphincter.

Summary

The effect of the alpha-adrenergic blocking agent, phentolamine, was studied on the perineal muscle EMG in 3 paraplegic patients. The drug reduced the EMG activity in these patients. This suggests that the normal suppression of external sphincter activity during micturition might be related to a reduction in the external sphincter activity supplied by the sympathetic system.

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The Authors

John B. Nanninga, MD, Associate Professor of Urology, Northwestern University Medical School.
Paul Kaplan, MD, Attending Physician, Rehabilitation Institute of Chicago.
S. Lal, MD, Attending Physician, Rehabilitation Institute of Chicago.

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Short Case Report

Transitional Cell Carcinoma and Schistosomiasis in a 5-Year-Old Boy

Transitional cell carcinoma of the urinary bladder is a rare tumour in childhood. When Ross, Wogalter and Spatz (1967) reviewed the literature, only 11 cases had been recorded. The association of schistosomiasis and bladder tumours has been well documented and El-Badawi (1966) reported an incidence of bilharzial papilloma in 7·2% of 1,196 bilharzial patients.

Case History

A 5-year-old Liberian boy presented with a 6-month history of intermittent terminal haematuria. He had already received treatment for bilharziasis with Niridazole (Ambilhar) but his symptoms had recurred. Physical examination revealed a distended bladder due to clot retention. Urine examination showed albuminuria, a few white cells and *S. haematobium*. There were hook-worm ova in the faeces. Excretion urography showed normal upper urinary tracts, but the bladder film showed a filling defect on the left lateral wall (Fig. 1). At cystoscopy there was a tumour 1 × 2 cm which was covered with calcified debris and blood clot. A partial cystectomy was performed and the tumour was found to be a transitional cell carcinoma, Grade I, with schistosomiasis (Fig. 2). He has remained well and there is no evidence of recurrence when examined after 12 months.

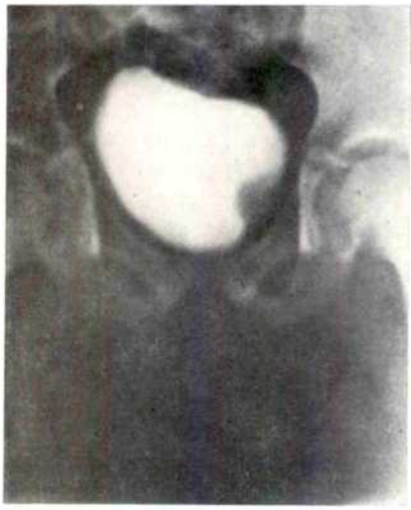

Fig. 1

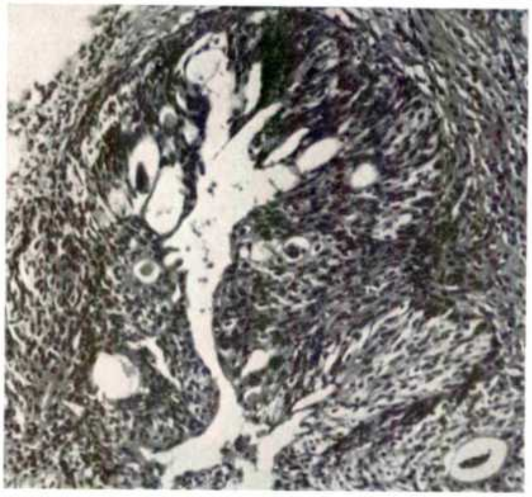

Fig. 2

Comment

The prognosis for patients with malignant bladder tumours and schistosomiasis is generally poor (Boulkany *et al.*, 1972). Although there are so few reported cases in childhood, those with well differentiated tumours have shown no evidence of recurrence when followed for 6 to 7 years.

W. Brumskine, P. Dragan and L. Sanvee
John F. Kennedy Memorial Hospital, Monrovia, Liberia

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Serum Dihydrotestosterone in Patients with Benign Prostatic Hypertrophy

R. GHANADIAN, J. G. LEWIS, G. D. CHISHOLM and *E. P. N. O'DONOGHUE

Prostate Research Laboratory, Urological Unit, Royal Postgraduate Medical School, London W12; and Institute of Urology, London WC1*

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There is good evidence to show that the level of circulating testosterone in normal men declines with age and that this change becomes more apparent in the 6th decade of life (Vermeulen, Rubens and Verdonck, 1972; Pirke and Doerr, 1973; Stearns *et al.*, 1974). Recently, it has been demonstrated that serum 5α-dihydrotestosterone also decreases with age (Lewis, Ghanadian and Chisholm, 1976). Unlike testosterone, the main source of this metabolite of testosterone is not the testis; more than 70% of circulating dihydrotestosterone in man originates from the peripheral conversion of testosterone (Ito and Horton, 1971; Mahoudeau, Bardin and Lipsett, 1971), about 15% is converted from androstenedione (Tremblay *et al.*, 1972) and only a small fraction is secreted by the testis.

Dihydrotestosterone has been reported to be the main androgen in the prostate (Ghanadian, 1976) and it is known that the level of dihydrotestosterone in benign hypertrophied prostate is 4 to 5 times greater than in the normal gland (Siiteri and Wilson, 1970).

This study was designed to investigate the changes in the circulating blood level of dihydrotestosterone and testosterone in patients with benign prostatic hypertrophy.

Materials and Method

24 normal men and 25 patients with benign prostatic hypertrophy (BPH) were studied. Normal men were chosen from a screening unit where they had attended for a routine medical examination. They were all in good health with no relevant general medical or urological symptoms or signs. The clinical diagnosis of BPH was confirmed in all patients by histological examination of the operative specimen. The age range for subjects and patients with BPH was 60 to 80 years; the mean ± S.E.M. in normal subjects and patients with BPH was 66·2 ± 0·94 and 68·0 ± 1·31 years respectively.

Venous blood was drawn between 10 a.m. and mid-day. The serum was separated and stored at −20°C prior to assay. Testosterone (T) and 5α-dihydrotestosterone (DHT) was measured by a radioimmunoassay (RIA) technique developed in our laboratory (Ghanadian, Lewis and Chisholm, 1975). The sensitivity of the RIA method was 5 and 10 pg for T and DHT respectively. The within-assay variance evaluated by 6 duplicate determinations on human pooled serum gave a coefficient variation of 11·6% and 6·5% for T and DHT. The between-assay variation for 8 determinations was 9·2% and 6·5% for T and DHT respectively. The mean recovery for T and DHT was 62 ± 1% (S.E.M.). Blanks were always undetectable and if known pools of human serum read more than 2 standard deviations from the mean the assay was repeated.

Results

Serum 5α-dihydrotestosterone was measured in 25 patients with BPH: the mean ± S.E.M. was 81 ± 4 ng/100 ml (2·79 ± 0·13 nmol/l). The corresponding value for the 24 normal men was 67 ± 3 ng/100 ml (2·30 ± 0·10 nmol/l). Statistical analysis of the results (unpaired T test) showed a significant difference between these two groups ($P < 0{\cdot}02$). Further analysis of these data using the Wilcoxon rank test showed a median for serum dihydrotestosterone of 75 ng/100 ml (2·58 nmol/l) in patients with BPH and 65·50 ng/100 ml (2·25 nmol/l) for normal men. The difference between the two groups was significant ($0{\cdot}01 < P < 0{\cdot}05$).

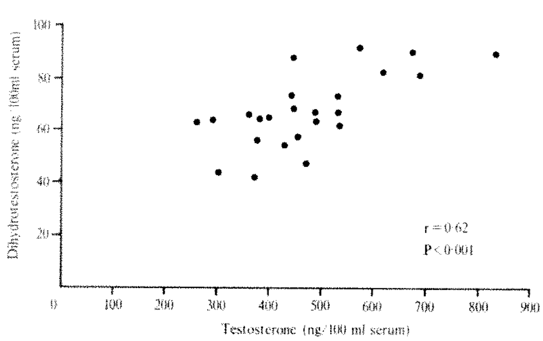
The level of serum testosterone in these 2 groups did not differ significantly. The value for serum testosterone in BPH was 438 ± 27 (mean ± S.E.M.) ng/100 ml (15·19 ± 0·97 nmol/l). The corresponding value in the normal men was 475 ± 28 ng/100 ml (16·47 ± 0·97 nmol/l). There was no significant difference between these two groups ($P > 0{\cdot}1$).

The serum T/DHT ratio in normal men was found to be 7·1 ± 0·3 (mean ± S.E.M.), whereas in patients with BPH this ratio decreased to 5·50 ± 0·3. There were significant correlations between serum testosterone and dihydrotestosterone in normal men ($P < 0{\cdot}01$) as well as patients with BPH ($P < 0{\cdot}01$) (Figs 1 and 2).

Discussion

The present study has demonstrated an increase in DHT in patients with benign prostatic hypertrophy when compared to matched control men. There was a wide variation in the DHT level of individual patients and some overlap in 2 groups. However, the overall results showed a statistically significant difference between normal subjects and patients with BPH.

Mahoudeau, Delassalle and Bricaire (1974) have reported that the level of DHT in venous blood draining from an enlarged prostate is higher than in the peripheral blood, but the mean value for peripheral DHT in the BPH group did not differ from that of the age-matched control group. Horton *et al.* (1975) found a significantly higher circulating DHT level in patients with BPH aged 60 to 90 years but their comparison was with a group of normal men aged 20 to 40 years. The concentration of DHT in the prostatic tissue of patients with BPH is known to be significantly higher than the concentration in the normal gland; the peri-urethral area of the normal gland which is prone to benign hypertrophy contains a higher level of DHT than the outer regions of the gland (Siiteri and Wilson, 1970). It is possible that the high level of circulating DHT in patients with BPH may be due to some contribution of this steroid from the prostate.



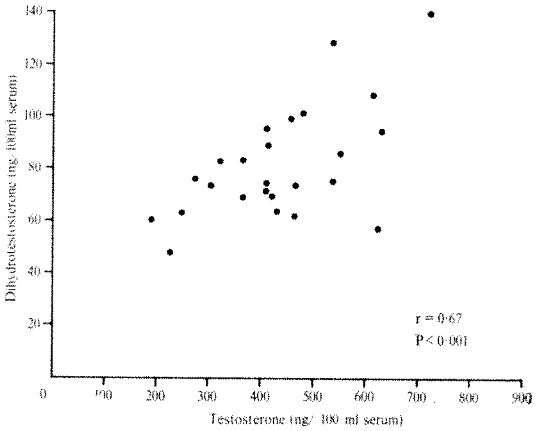


Fig. 1. Correlation between the level of dihydrotestosterone and testosterone in normal subjects.

Fig. 2. Correlation between the level of dihydrotestosterone and testosterone in patients with benign prostatic hypertrophy.

However, based on the present study, it is not possible to determine the amount of DHT which originates from prostatic secretion or from the peripheral conversion of the other steroids. In contrast with DHT, the level of testosterone in patients with BPH remains the same as normal controls. This is, however, a significant fall in the testosterone level of this group when compared with younger age-groups (Lewis, Ghanadian and Chisholm, 1976).

Although the present data show a *statistically* significant increase in the serum DHT in patients with BPH, the scatter of values in individual patients is such that the measurement of this hormone would have little application in either diagnosing or monitoring prostatic enlargement. Wilson and Siiteri (1970) have measured the DHT *formation* (expressed as $\mu\mu$ moles/15 mg/hour) by prostate slices and have shown no differences in formation as the weight of the gland increases. In our study we made no attempt to correlate the weight of the gland with the level of serum DHT but it may be that there is an increase in DHT *output* as the gland enlarges.

The measurement of serum hormone levels has become much more relevant in unravelling the aetiology of BPH (Farnsworth, 1976). The paradox of decreasing testicular function with age, as judged by the serum levels of testosterone, and increasing prostatic growth indicated that testosterone might not be the active hormone for prostatic growth. The demonstration that DHT is the principal intracellular androgen and that it is concentrated in hypertrophied tissue suggested that this hormone has a central role in the metabolic process for the growth of the prostate. However, in an experimental study, the administration of DHT alone to castrate dogs did not induce prostatic hypertrophy but dogs that received a combination of androstanediol (a metabolite of DHT) and oestradiol all developed hypertrophy (Walsh and Wilson, 1976). This experimental observation adds support to the view that an alteration in androgen and oestrogen concentrations, and possibly changes in receptor responses in the prostatic cell that occur with age, are the main factors that allow the gland to hypertrophy in later life.

Summary

Serum dihydrotestosterone (DHT) and testosterone were measured by radioimmunoassay in 24 normal men aged 60 to 80 years and in 25 patients with benign prostatic hypertrophy in the same age range.

There was a significant increase in the level of dihydrotestosterone in patients with prostatic hypertrophy but no significant difference was found between the testosterone levels of the 2 groups.

The scatter of the individual values for DHT indicated that this measurement has little practical clinical application in the diagnosis of prostatic hypertrophy.

It is suggested that the increase in DHT may be due, at least in part, to a prostatic contribution to the circulating level and the relevance of this observation in relation to the aetiology of benign prostatic hypertrophy is discussed.

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The Authors

R. Ghanadian, PhD, Lecturer and Research Fellow.
J. G. Lewis, MSc, Biochemist.
G. D. Chisholm, ChM, FRCS, Consultant Urological Surgeon and Senior Lecturer.
E. P. N. O'Donoghue, FRCS, Senior Lecturer.

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The Anatomy of the Urethral Stricture

R. M. CHAMBERS and B. BAITERA
Department of Surgery, Makerere University Medical School; and Mulago Hospital, Kampala, Uganda

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Little is known of the pathology of acute gonococcal urethritis and even less of the anatomical changes that follow and which eventually may lead to the development of a urethral stricture. A few men develop a stricture within months of infection, but for the majority it is several years before urinary symptoms demand treatment. There is no way of finding out what is happening in the urethra during this long latent period unless the man dies of some other cause and the urethra be specially examined. In most countries, gonorrhoea is not common enough for this to be practicable.

Similarly, the descriptions of the anatomy of the established stricture are few and inadequate. For the most part, information has been obtained from biopsies and attention has been focused on the stricture alone. Beard and Goodyear (1948) described the dense scar tissue of the stricture, the thin overlying epithelium and the notable absence of acute inflammatory reaction except at the proximal end of the stricture. They suggest that chronic infection is the probable cause but neither they, nor anyone else, have been able to demonstrate bacteria in the urethra in uncomplicated strictures (Marcus, 1966).

In Uganda, gonorrhoea is endemic at a very high rate and the medical and social complications are enormous. In 1948, over 12,000 new cases were seen in the Out-patients Clinics at Mulago Hospital, Kampala (McAdam, Burkitt and Ladkin, 1949) and in 1963 Griffith recorded that about 20% of sexually active males contracted gonorrhoea at least once a year. In 1969, complicated urethral stricture was the reason for 20% of all non-traumatic surgical admissions to Mulago Hospital and over 800 new patients were seen at the Stricture Clinics (Uganda Health Department, 1969).

There is in Uganda a unique opportunity to study the effects of gonococcal urethritis. This paper reports the results of an anatomical study of the male urethra from a random series of autopsy examinations during 1969. Nearly all specimens bore the scars of previous gonorrhoea and half had established strictures.

Method

22 specimens of urethra, prostate and bladder were removed intact at routine autopsy examinations performed at Mulago Hospital during 1969. In order to have a normal standard for comparison, the urethra of a boy aged 8 years was obtained. He had died of trauma and had no known urinary complaint.

Each specimen was first inflated to about 20 cm water pressure with Urografin 30% and X-rayed to determine whether a stricture was present or not. It was then fixed in the distended state and divided down the middle. Blocks of tissue were taken at 1 cm intervals from the glans penis to the bladder neck, and representative sections were stained with Haematoxylin and Eosin, Mallory's trichrome and Gram stains.

Results

3 specimens were considered normal, *i.e.* similar to that of the 8-year-old boy, and these came from men aged 22, 48, 67 years. It was deduced that the normal histology did not alter with

increasing age. 8 specimens had visible mucosal abnormalities without stricture and 11 specimens had obvious strictures. These varied in calibre from minimal narrowing to complete occlusion, and in length from a simple diaphragm to a lesion involving the entire spongy urethra. The occluded stricture had an established fistula to the perineum.

The Normal Urethra (Fig. 1)

A brief description of the normal histology is included to emphasise aspects of importance to the present study.

The lumen was lined by pseudo-stratified columnar epithelium (Ham, 1969) from the fossa navicularis to the membranous urethra. Small islands of non-keratinised squamous epithelium were seen near the meatus but were not found more than 5 cm proximally. There were numerous mucosal glands in the surface epithelium along the whole spongy urethra but peri-urethral glands were sparsely scattered, and their long ducts slanted proximally deep into the spongy tissue.

There was no muscularis mucosa or other support for the surface epithelium. A thin layer of loose connective tissue separated the mucosa from the spongy tissue, and the smooth muscle of the spongy tissue was oriented around the blood sinuses rather than the urethral lumen. The

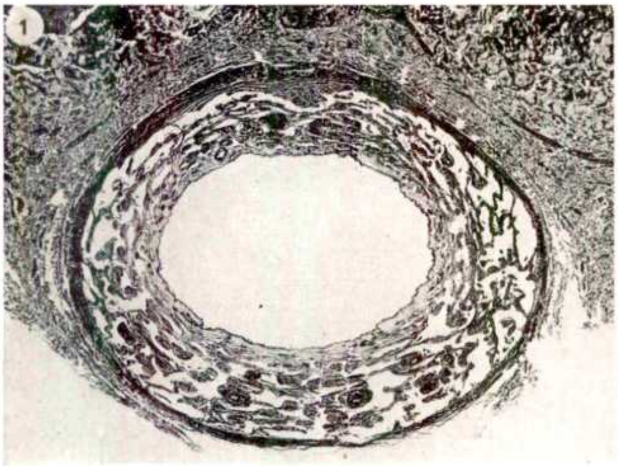


Fig. 1. Normal penile urethra. Trichrome × 10.

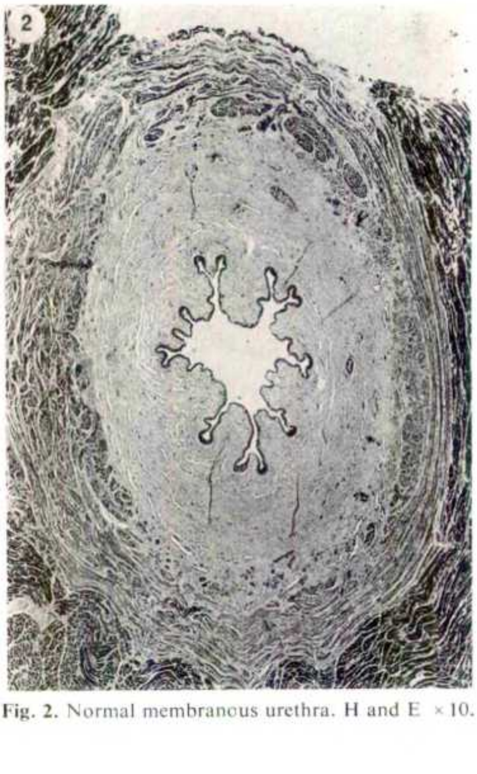


Fig. 2. Normal membranous urethra. H and E × 10.

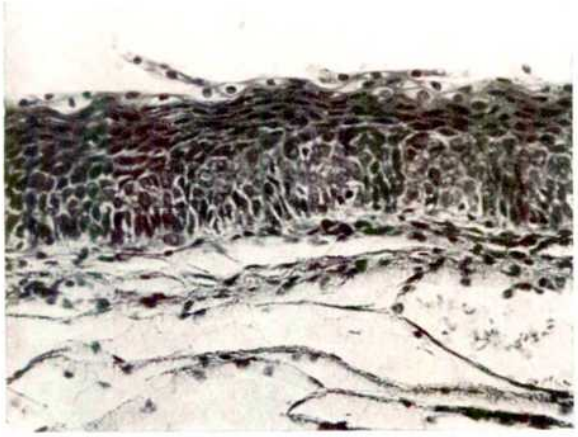
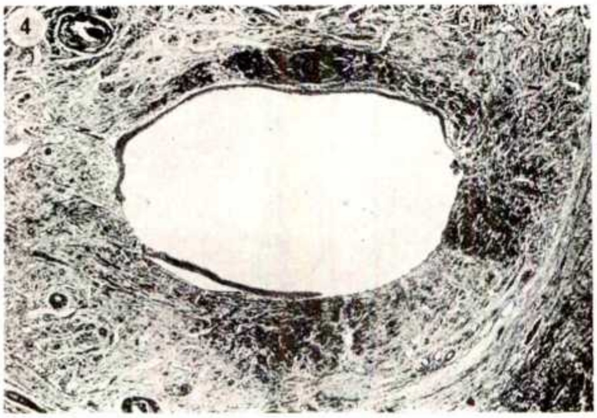


Fig. 3. Metaplastic squamous epithelium in abnormal urethra. H and E × 60.

lumen was thus able to dilate easily at low pressure until limited eventually by the thick sleeve of collagen which enclosed the spongy tissue. This sleeve, the tunica albuginea, increased in calibre from about 1 cm in diameter along the penis to about 3 cm back at the urethral bulb.

The bulbous spongiosus muscle (ejaculator muscle) arched forward from its origin on the perineal membrane to surround the perineal urethra. It seemed capable of exerting considerable compression on this portion of the urethra.

Through the membranous urethra (Fig. 2), the anatomy changed considerably. The epithelium became transitional as in the bladder and a thick submucosa of loose collagen and elastic fibres replaced the blood sinuses of the spongy urethra. Prominent layers of smooth muscle (inner longitudinal and outer circular) spread up from the perineal membrane into the prostate, apparently bringing the lumen under muscular control. Mucosal glands and peri-urethral glands were still seen and the bulbo-urethral glands (of Cowper) lay in the outer part of the striated urethral sphincter.



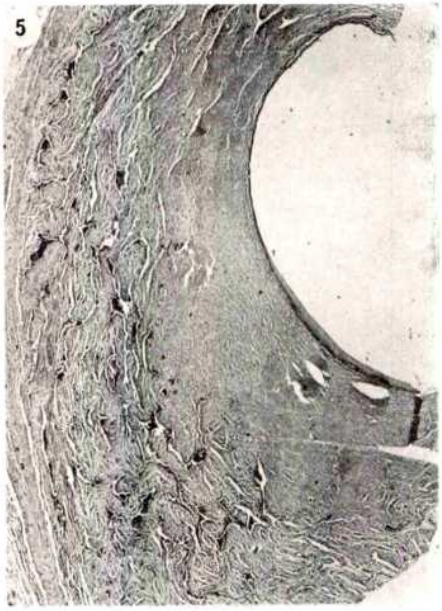
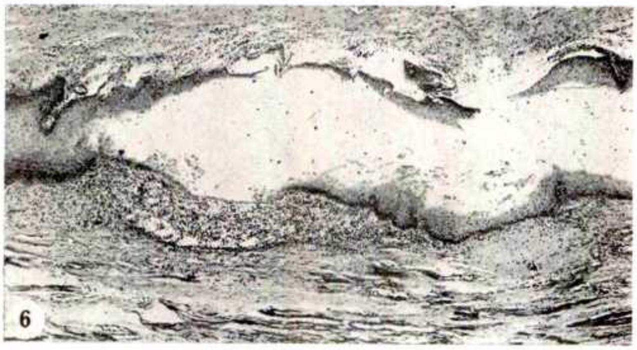


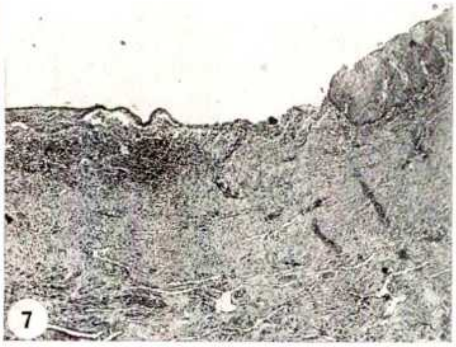
Fig. 4. Post gonococcal submucosal scars beneath squamous epithelium. Trichrome × 10.

Fig. 5. Post gonococcal scars. Large collagen scar with overlying squamous epithelium. H and E × 10.

Fig. 6. Mucosal ulcers in squamous epithelium. Acute ulcer on left, new collagen on right. H and E × 40.

Fig. 7. Acute mucosal ulcer. H and E × 40.





The Abnormal Urethra

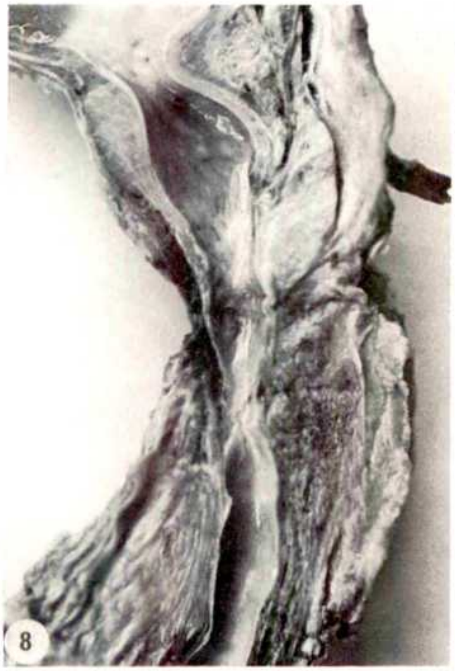
8 specimens had mucosal lesions without visible or radiological narrowing of the lumen. In each case the abnormality was most marked in the perineal urethra.

In 2 specimens (age 18, 29 years), the visible lesions were numerous white scars in an otherwise translucent mucosa. 2 others (age 30, 48 years) had several larger white plaques in generally opaque mucosa, and in the other 4 specimens (age 22, 31, 48, 64 years) the whole urethral surface was thick and white from the perineal membrane forwards for several centimetres. In 2 there were patches of pigmentation.

Microscopic examination revealed similar abnormalities in all specimens. Much of the lumen was now lined by squamous epithelium (Fig. 3). This was thin, flat and not keratinised, and extended well beyond the area of visible abnormality. All mucosal glands had gone, but normal peri-urethral glands were still seen deep in the spongy tissue.

Just beneath the epithelium lay the scars, varying in size from small scattered foci (Fig. 4) to large, almost circumferential plaques (Fig. 5). They rarely extended deep into the spongy tissue and were not seen in or around the peri-urethral glands or ducts. The collagen was mature, and had few inflammatory cells in or around it.

The most important finding in these specimens was the occasional microscopic ulcer in the surface epithelium (Fig. 6). 1 or more ulcers were eventually found in 5 of these 8 specimens after careful search, and were seen in all stages of formation and repair. In the earliest lesions (Fig. 7) it appeared that the epithelium had pulled apart, for it was cleanly separated and had retracted, leaving a bare area in which an early inflammatory reaction was present. No ulcer contained slough or bacteria. Some showed signs of repair with re-epithelialisation and immature collagen. These ulcers were seen only in squamous epithelium and none lay over a mature scar.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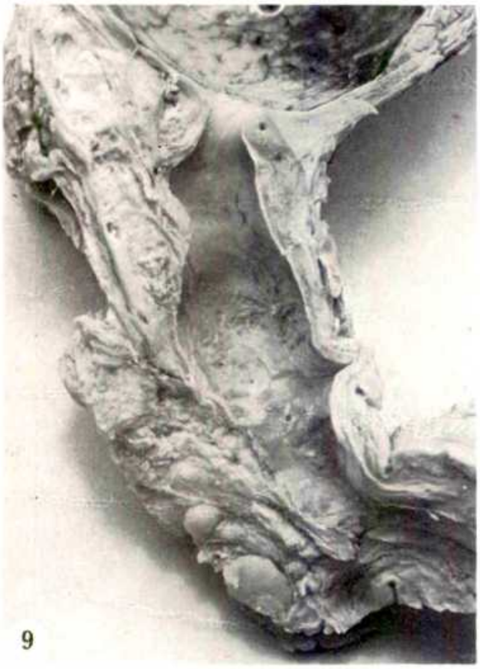
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Fig. 8. Perineal urethral stricture—sagittal section. Separate distal large calibre ring, tapering stricture, proximal dilatation.

Fig. 9. Proximal dilatation above stricture. Large mucosal ulcers.

The Urethral Stricture

11 specimens had demonstrable urethral strictures. By X-ray assessment before fixing, the strictures varied from a 2-mm diaphragm to a 10-cm multiple stricture with fistula. There was always proximal dilatation extending up through the membranous urethra to the bladder neck. Dye was seen to reflux into prostatic ducts and cavities in most specimens.

The macroscopic appearances varied considerably in different specimens but a typical pattern was evident (Fig. 8). Beyond the most distal ring of the stricture the lumen was smooth, opaque and only occasionally pigmented.

The stricture was usually a series of rings of scar tissue which became successively tighter and thicker as the lesion extended proximally. In some, the rings were spaced over several centimetres and in others they were almost confluent, but the top ring was usually the tightest and most dense. Above the stricture the lumen became dilated, the mucosa was thick and pale, and often had areas of hyperkeratosis and pigmentation. Two specimens bore large superficial ulcers in the dilated upper segment (Fig. 9).

The microscopic changes were an extension of those seen in the pre-stricture stage. Squamous epithelium lined the whole of the spongy urethra and occasionally extended well up into the prostate. Distal to the stricture the epithelium was thin, smooth and not keratinised, and there was minimal inflammatory activity and no mucosal ulcers or recent scars were seen. Through the stricture, the epithelium was thin and smooth but it was always intact. The scar tissue was dense, mature and often hyalinised, but there was minimal inflammatory infiltration. It appeared stable (Fig. 10).

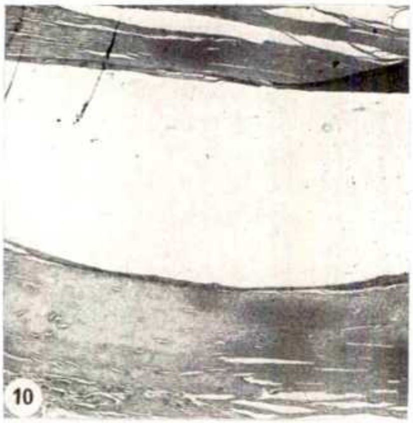
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Fig. 10. Urethral stricture—sagittal section. Mature collagen, minimal inflammation. H and E ×25.

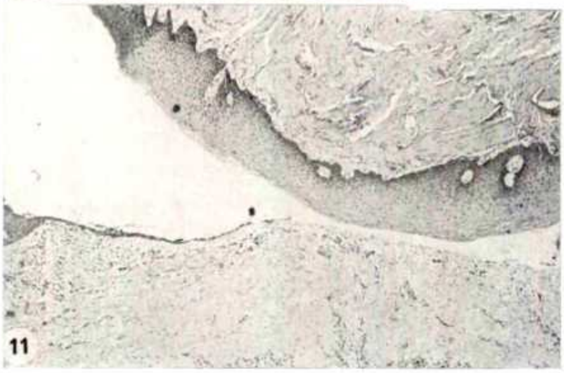
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Fig. 11. Urethral mucosal ulceration above stricture. Dysplastic squamous epithelium with pigmentation and keratinisation. H and E ×40.

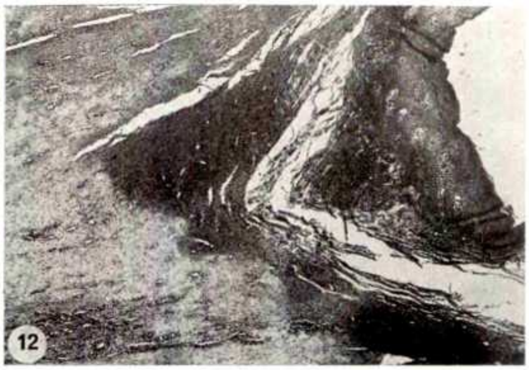
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Fig. 12. Urethral stricture, proximal face. Sagittal section. Hyperplastic epithelium, sub-epithelial inflammation and new collagen. H and E ×40.

By contrast, above the stricture there was always considerable inflammatory activity. The squamous epithelium was much thicker, always keratinised and often pigmented (Fig. 11). In some areas it resembled epidermis. In 3 specimens there were areas of epithelial dysplasia and in one a patch of carcinoma *in situ*. Beneath the mucosa, inflammation and new collagen were seen everywhere, particularly at the proximal face of the stricture (Fig. 12). Mucosal ulcers were common and often large, but bacteria and slough were not seen except in the specimen with the external fistula. The few remaining peri-urethral glands were dilated and often inflamed.

In the specimen with a fistula, there was obvious bacterial infection in the urethra above the stricture and in the prostate. Mucosal ulceration was extensive, with slough in the base of some ulcers and abscesses in the peri-urethral glands. Dysplastic squamous epithelium was present around the internal orifice of the fistula track but the track itself was not epithelialised.

The change from squamous epithelium to normal epithelium usually occurred in the membranous urethra, but on two occasions squamous epithelium extended right up to the bladder. Extensive pathology was commonly seen in the prostate gland, but this will be described in a subsequent paper.

Discussion

This series of specimens illustrates the development of the urethral stricture from the scattered scars which are presumed to be the legacy of previous gonorrhoea. It appears that the initial and fundamental change is metaplasia of the surface epithelium from the original pseudo-stratified columnar to stratified squamous epithelium. This squamous epithelium is relatively inelastic, and in other areas of the body has support to prevent overstretching. In the skin there is the dermis and in the oesophagus there is muscle, but the spongy urethra has only a thin loose stroma of connective tissue overlying blood sinuses. The unsupported epithelium probably overstretches occasionally during voiding and ruptures, a shallow ulcer forms, and then heals leaving a microscopic scar beneath the repaired epithelium. This scar will now protect the overlying epithelium to some extent, and the next rupture is likely to occur in an adjacent area.

Over the years the individual scars accumulate and eventually become confluent to form plaques of scar tissue. These plaques grow slowly until eventually at one point the lumen becomes encircled and a large calibre stricture is created.

Once a complete ring of collagen has formed the urine stream will impinge directly on it and the lumen above will dilate each time voiding occurs. This will increase stretching at the proximal face of the ring and cause further epithelial damage and inflammatory reaction. The stricture will grow proximally and will narrow by contracture forming its typical conical shape. The natural outcome of this process is for the stricture to tighten to occlusion.

It seems that apart from the initial gonococcal infection which induces the squamous metaplasia in the urethral lumen, bacterial infection plays no part in the development of a stricture. It is possible that in those patients who deny previous gonorrhoea, areas of squamous epithelium remain in the urethra at birth or that as a result of distal obstruction (*e.g.* meatal stenosis) high voiding pressure alone could induce epithelial metaplasia. In either case a stricture might then appear without infection at all.

The complications that follow urethral stricture can also be readily explained by these findings. Extensive rupture above a stricture may allow urine to leak out through the spongy tunica albuginea during voiding, to form a collection in the subfascial tissue. If the leak remains open extensive urinary extravasation will occur and if infection supervenes a peri-urethral abscess will develop. Finally it is likely that the continued inflammation and ulceration of the squamous epithelium probably induces leukoplakia and squamous carcinoma in the urethra above the stricture in many of these patients.

Summary

A post-mortem study of the urethral anatomy following gonorrhoea is presented. The different specimens examined demonstrated lesions ranging from microscopic submucosal scars to fully developed urethral strictures. In every specimen extensive squamous metaplasia of the surface epithelium was present. It is postulated that overstretching of this unsupported squamous epithelium during voiding causes microscopic epithelial tears and that the accumulation of the subsequent microscopic scars leads to the formation of a urethral stricture. Bacterial infection does not seem to play any part in the genesis of the stricture.

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Photomicrographs supplied by Auckland Hospital Photographic Department.

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The Authors

R. M. Chambers, FRACS, FRCS. Urologist, Mulago Hospital, Kampala (now visiting Urologist, Auckland Hospital, Auckland).

B. Baitera, MB, BS., House Surgeon, Mulago Hospital.

Reprints from R. M. Chambers, Department of Urology, Auckland Hospital, Park Road, Auckland 3, New Zealand.

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Short Case Report

Retroperitoneal Fibrosis following Aortic Surgery

Case Report

A 65-year-old man presented with symptoms of prostatism and tiredness. Past history included an aorto-aortic graft for a leaking aneurysm 2 years previously. He had an enlarged prostate, residual urine and was uraemic. Urography showed bilateral hydronephrosis with poor visualisation of the ureters.

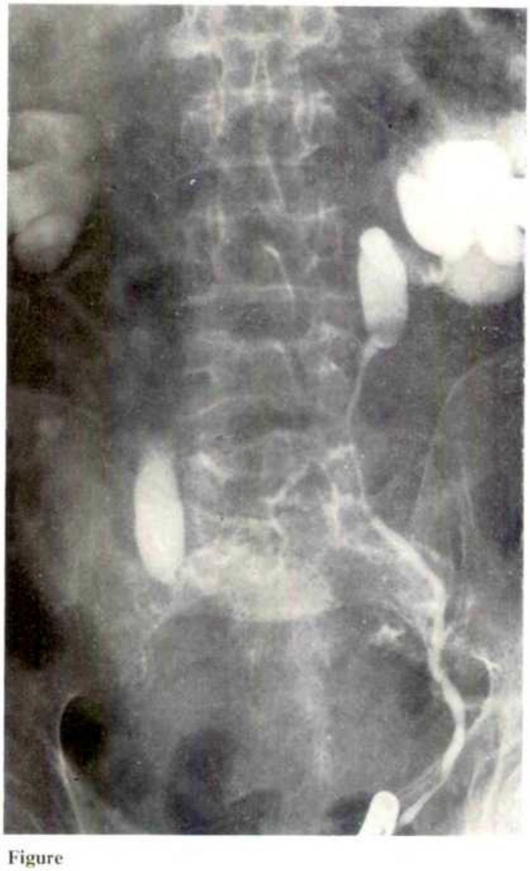
Transurethral prostatectomy did not improve his renal function and ureterography suggested retroperitoneal fibrosis (Fig.). Ureterolysis was performed but was made difficult by ignorance of the relationship of the aortic graft to the ureter. Histology showed no evidence of malignancy but considerable infiltration of the fibrous tissue with haemosiderin.

Discussion

Lytton (1966) described 2 cases of ureteric obstruction following aorto-iliac surgery and since the obstruction was where the graft crossed the ureter thought that the cause was the recurrent pulsation. This did not apply in this case and the presence of the haemosiderin suggests that organised haematoma has resulted in the fibrosis. A case may be made for routine urography after aorto-iliac surgery.

When grafts are placed to the common iliac artery the ureter usually remains anterior but grafts to the external iliac or femoral artery are placed in front of the ureter. Since dissection in the region of a graft is difficult and dangerous it may be advisable to divide the ureter and perform an end-to-end anastomosis.

J. R. Rhind
Bradford Royal Infirmary, Duckworth Lane, Bradford, West Yorkshire BD9 6RJ



Figure

Reference

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Advances in the Management of Non-seminomatous Germinal Tumours of the Testis

DONALD G. SKINNER

Department of Surgery, Division of Urology, UCLA School of Medicine, Los Angeles, California 90024

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Controversy continues to rage over the best method of treatment of non-seminomatous germinal tumours of the testis. Most British urologists continue to extol the virtues of radiation therapy as single modality treatment (Blandy, Hope-Stone and Dayan, 1970; Smithers, Wallace and Wallace, 1971; Blandy, 1976; Smithers, 1976). American urologists base their management plan on lymph node dissection (Whitmore, 1970; Walsh *et al.*, 1971; Staubitz *et al.*, 1974; Skinner, 1976a) but often combine other forms of adjuvant treatment such as chemotherapy and occasionally post-operative radiation therapy.

Much of the confusion and controversy stems from the following factors:

(1) Classification of these tumours has not been uniform and is inadequately understood. Table I, which compares the British classification with the one most commonly used in the United States, demonstrates that a comparison of survival figures between the 2 classifications is practically impossible. For instance, M.T.I.B.[1] comprises a group of tumours neither similar nor comparable to any one group in the American classification inasmuch as it combines embryonal tumours demonstrating epithelial differentiation with those also containing primitive tridermal components such as primitive cartilage, loose groups of muscle cells or fatty tissues (Pugh and Smith, 1964). This latter group of tumours would be classified as teratocarcinoma according to

Table I

Non-seminomatous Germinal Cell Tumours of the Testis

Classification			
Pugh, 1971	Collins and Pugh, 1964		Friedman and Moore, 1946 Teilum, 1971
M.T.I.	M.T.I.A.		Teratocarcinoma
M.T.U.	M.T.I.B.	More differentiation containing structures of tridermal character (Primitive cartilage, muscle, vascular, etc.)	
		Identifiably epithelial with early differentiation but without any tridermal or teratoid components	Embryonal carcinoma
	M.T.A.		
M.T.T.	M.T.T.		Choriocarcinoma

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[1] M.T.I.B. = Malignant Teratoma Intermediate, Group B.

Table II

3-Year Crude Survival Rates according to Cell Type (Skinner, 1976a)

Cell type	Survival No.	Survival %
Embryonal	28/36	78
Mixed	9/13	69
Teratocarcinoma	45/57*	81
Mixed	12/16	75
Choriocarcinoma	1/2	–
Chorio elements	10/14	71
Seminoma elements	13/17	77

* One operative mortality excluded.

Friedman and Moore (1946) even though they do not contain mature tissue or demonstrate organoid differentiation. Therefore, Pugh's proposal to include the M.T.I.B. and M.T.A.[1] groups under the term "malignant teratoma, undifferentiated (M.T.U.)" does not help resolve the problem (Pugh and Cameron, 1976). One additional area of distinction concerns choriocarcinoma vis-à-vis malignant teratoma, trophoblastic (M.T.T.). Both classification systems recognise that strict histological criteria are required to warrant either diagnosis; 2 cellular components, syncytiotrophoblastic and cytotrophoblastic cells, must be readily identified and arranged in a papillary or pseudovillous pattern (Friedman and Moore, 1946; Pugh and Smith, 1964). According to the latter authors, the term "malignant teratoma, trophoblastic" includes pure choriocarcinoma as well as mixed tumours which consist of a focus of choriocarcinoma and one or more other cell types. In Friedman and Moore's (1946) classification, these latter mixed tumours would be grouped in the teratocarcinoma or more usual embryonal carcinoma category, depending on the histology of the rest of the tumour, a concept which correlates with their biological behaviour. Therefore, until pathologists can agree on an international classification system, clinicians will continue to argue and camouflage their results in a maze of small, diverse groups dependent on classification rather than success of any management plan.

Nevertheless, several points should be noted. If pure choriocarcinoma is excluded, it is evident that tumour cell type has far less influence on survival than method of treatment (Skinner, 1976a). A recently published series of 96 consecutive patients with all stages and all cell types indicates that survival is not statistically influenced by cell type. The series comprised patients with pure embryonal carcinoma, teratocarcinoma and mixtures with seminoma and/or choriocarcinoma (Table II) (Skinner, 1976a). Experimental data support Friedman's contention that germinal tumours of the testis arise from totipotent primordial germ cells and that there is a natural tendency toward maturation or the development of adult teratomatous tissue (Stevens, 1960, 1967; Pierce, 1966; Pierce and Abell, 1970; Friedman, 1976). There are also clinical reports of extremely primitive anaplastic primary tumours metastasising as adult mature teratomas, often following or associated with chemotherapy (Snyder, 1969; Skinner, Leadbetter and Wilkins, 1971; Comisarow and Grabstald, 1976). Whether this phenomenon represents the effect of chemotherapy or the natural history of the tumour remains in question.

(2) It has only recently been documented that lymph node dissection can effectively remove the retroperitoneal nodes (Kaswick, Bloomberg and Skinner, 1976), but indiscriminate use of post-operative radiation therapy, in most surgical series, has made it difficult to evaluate the contribu-

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[1] M.T.A. = Malignant Teratoma, Anaplastic.

Table III

Initial In-patient Course of Chemotherapy given to Patients with Disseminated Disease (Stage C) or Clinical Evidence of Massive Retroperitoneal Disease (Skinner, 1976)

In-patient chemotherapy		
Day No. 1	Actinomycin D	1·0 mg IV over 3 hours
	Cytoxan	2·0 mg/kg wt. IV
	Methotrexate	5·0 mg IV
Day No. 2	Repeat actinomycin D	
	Repeat cytoxan	
Day No. 3	Repeat actinomycin D	
	Repeat cytoxan	
	Repeat methotrexate	
Day No. 4	Repeat actinomycin D	
	Repeat cytoxan	
	Vincristine	2·0 mg IV
	Prednisolone	20·0 mg P.O.*
Day No. 5	Repeat actinomycin D	
	Repeat cytoxan	
	Repeat methotrexate	
	Repeat prednisolone	
Day No. 6	Actinomycin D	0·5 mg IV
	Repeat prednisolone	

* Prednisolone used to reduce toxicity.

Table IV

3-Year Survival Rates for All Patients According to Pathologic Stage

	Survival		
Stage	No.	%	
A	39/43	91	67/79—85%
B_1	12/14*	86	
B_2	16/22	73	
C	8/17†	47	
Total	75/96	78	

* One death—operative mortality.
† One death—suicide 18 months post-operatively; no evidence of tumour at autopsy.

tion of lymphadenectomy to improved survival. Reports by several authors document that lymph node dissection alone can effectively deal with retroperitoneal metastatic disease (Walsh *et al.*, 1971; Staubitz *et al.*, 1974; Skinner, 1976a). Long-term follow-up, however, reveals that seemingly regional metastatic disease may be systemic, thus emphasising the need for adjuvant systemic chemotherapy (Walsh *et al.*, 1971; Skinner, 1976a). Concern over loss of fertility secondary to lymph node dissection is probably not justified. A recent study at UCLA Hospital demonstrates that a significant number of patients with non-seminomatous testicular cancer were severely oligospermic before any form of therapy, and thus infertile regardless of ejaculatory ability. If semen analysis before therapy demonstrates adequate sperm quantity and quality semen, cryopreservation has been encouraged for possible subsequent artificial insemination (Skinner and LaNasa, 1976).

(3) Inasmuch as patients with testicular tumours are rare, it is difficult to develop a plan of management, and thus there is a tendency for 1 therapeutic modality to predominate, with minimal interest in a combined approach. Recent co-operative developments at several institutions in the United States have documented the fact that there are now at least 3 potent cytotoxic agents available to the urological oncologist which profoundly affect all types of non-seminomatous tumour of the testis. Moreover, our experience with the most extensive and advanced disease indicates that combination chemotherapy has dramatically altered the outlook for long-term survival in such individuals (Donohue, 1976; Merrin *et al.*, 1976; Skinner, 1976b; Notwithstanding this, surgical resection of bulk disease is usually mandatory to effect a cure (Skinner, 1976b).

(4) Accurate staging is difficult unless surgical lymphadenectomy is performed; moreover, many reports exclude advanced cases, thereby making biased patient selection an important factor in survival statistics.

Patients and Management

This report is based on the treatment and results of 96 consecutive patients without exclusion, including 17 with Stage C disease together with a further 50 patients followed for less than 3 years.

Patients who presented with pulmonary metastases (Stage C) or clinical evidence of massive retroperitoneal disease were initially treated by a course of intensive in-patient chemotherapy (Table III), followed 2 to 3 weeks later by a 5-week out-patient course of bleomycin (30 units I.M. twice weekly for 5 weeks, 300 units total) and vinblastine sulfate (10 mg I.V. day 1; 15 mg I.V. day 8; 20 mg I.V. day 22). Retroperitoneal lymph node dissection was then performed 2 to 3 weeks later to remove bulk disease.

The retroperitoneal lymph node dissection was usually made through the thoraco-abdominal approach which allowed wedge resection of ipsilateral pulmonary metastases, a careful evaluation of the mediastinum, and complete removal of all retroperitoneal metastatic disease. All patients in this series underwent resection even for extensive tumour, which occasionally involved removal of the vena cava or an ipsilateral kidney.

Chemotherapy was considered the primary adjuvant, following lymphadenectomy, with actinomycin D being the basic drug. Dosage was based on the patient's weight and was given intravenously once a day for 5 days in each treatment course (for weight greater than 180 pounds: 5·0 mg over 5 days; 130 to 180 pounds: 4·0 mg over 5 days; under 130 pounds: 3·0 mg over 5 days). Early in our experience, chemotherapy was not generally used for patients with negative nodes, but now it is our policy to start a course of actinomycin D during operation, to continue it during the immediate postoperative period, and then repeat it once on a prophylactic basis 2 months later.

In patients who have pathologic Stage B_1 or more advanced disease, cyclic chemotherapy with actinomycin D is recommended every 2 months for the first year and every 3 months for the second year.

If the primary tumour contained foci of choriocarcinoma, if choriocarcinomatous elements were present in metastases, or if the patient had extensive retroperitoneal disease, at least 1 course of the combined vinblastine sulfate and bleomycin was substituted for the usual course of actinomycin D administered 2 months after lymphadenectomy.

Table V

3-Year Crude Survival Rates according to Adjuvant Therapy

	Stages					
	A-B_1		B_2		C	
Adjuvant Therapy	No.	%	No.	%	No.	%
None	18/22	82	1/1	–	1/1	–
Chemotherapy	28/30*	93	3/4	75	3/9	33
Radiation Therapy	4/4	–	3/7	43	0/2	–
Chemotherapy + Radiation	1/1	–	9/10	90	4/5†	80
Totals	51/57	89	16/22	73	8/17	47

* One Death—Operative mortality.

† One Death—Suicide 18 months postoperatively with no tumour present at autopsy.

Postoperative radiation therapy has been reserved for those patients who have extensive retroperitoneal disease, and only in those patients in whom disease was thought left behind. Beginning 4 to 6 weeks after lymph node dissection and after the immediate postoperative dose of chemotherapy, 4,500 rads are delivered to the retroperitoneum and ipsilateral iliac region. Four to 6 weeks after completing radiation therapy, chemotherapy is resumed on a cyclic basis every 2 months for the first year and every 3 months for the second year starting with 1 course of the vinblastine sulfate-bleomycin combination before continuing with actinomycin D.

Most patients with Stage C disease underwent a wedge resection of pulmonary metastases at the time of lymph node dissection or had a formal thoracotomy 3 to 6 months after lymph node dissection. These patients received a second full course of vinblastine sulphate and bleomycin after they had been rendered tumour-free by surgery, and cyclic chemotherapy was continued with actinomycin D for a full 2 years after their last surgical procedure.

Results

The three-year crude survival for all patients in this series was 78% (Table IV). In patients in whom the disease was confined below the diaphragm, the survival rate was 85%. One postoperative death occurred, representing a mortality rate of 1·3%.

The stage is directly related to the tumour-free interval and proved to be significant for survival; no patient had a recurrence more than 2 years after lymphadenectomy. In Stage A patients, the average time of tumour recurrence was 12 months and there was no recurrence later than 24 months after lymphadenectomy. In Stage B patients, the average time of tumour recurrence was 6 months, with no recurrence later than 12 months post-lymphadenectomy. Among Stage C patients, the average time of recurrence was 3 months, with a range of 0 to 9 months for recurrence. No patient in Stage C who was free of tumour for longer than 9 months after undergoing lymphadenectomy and wedge resection of pulmonary metastases or thoracotomy suffered a recurrence or died of disease.

Within each stage, chemotherapy improved survival, and therapy combining radiation, surgery and chemotherapy markedly improved survival for patients with advanced disease (Table V).

Discussion

Failure of surgical therapy is nearly always secondary to disseminated disease and the development of pulmonary metastases. In only 1 patient in our series with Stage A or Stage B disease did

Table VI

Non-seminomatous Testicular Tumours—Results of Surgical Therapy without Radiation—3-year Crude Survival Rate (%)

Stage	Author	Embryonal Ca	Terato Ca	Combined
A	Walsh *et al.*, 1972	10/10	14/15	24/25
	Staubitz *et al.*, 1974	27/30	15/15	42/45
	Skinner, 1976a	7/10	30/30	37/40
Combined		44/50 (88)	59/60 (98)	103/110 (94)
B	Walsh *et al.*	2/3	1/1	3/4
	Staubitz *et al.*	14/17	1/3	15/20
	Skinner	6/7	7/9	13/16
Combined		22/27 (81)	9/13 (69)	31/40 (78)
Total A+B		66/77 (86)	68/73 (93)	134/150 (89)

retroperitoneal recurrence develop; all other failures stemmed from pulmonary or disseminated disease. Based on this fact, it seems prudent to use a systemic agent which has known cytotoxicity against non-seminomatous tumours in an attempt to sterilise possible microscopic foci present beyond the field of surgical resection. Various cytotoxic drugs, in addition to actinomycin D, have been used as single agents or in combination: methotrexate, chorambucil, mithramycin, cyclophosphamide, adriamycin and vincristine (Mackenzie, Duruman and Whitmore, 1967; Ansfield *et al.*, 1969; Samuels and Howe, 1970; Kennedy, 1972; Monfardini *et al.*, 1972). Recently cis-platinum (II) diaminodichloride has shown considerable activity against these tumours and may prove an important agent in future use (Higby *et al.*, 1974; Donohue, 1976). It has substantial renal toxicity, however, and is currently being investigated. Actinomycin D remains the primary drug that seems most effective against the non-seminomatous group of testis tumours. Our experience with the combined use of vinblastine sulfate and bleomycin, supported by published reports by Samuels (1974) and by Samuels and associates (1970 and 1975) leads us to believe that it is extremely active against this group of tumours and we recommend it for all patients with extensive lesions or evidence of choriocarcinoma in the primary or metastatic tumour. However, because there is limitation to the total cumulative dose of bleomycin, long-term therapy requires resumption of cyclic actinomycin D therapy.

Early in our experience, prophylactic chemotherapy was seldom used for patients with Stage A or Stage B_1 disease, but results indicated that 18% of these patients developed pulmonary metastases. In other surgical series, the results have been similar, regardless of whether postoperative radiation therapy to the retroperitoneum was employed (Snyder, 1969). When failure occurs, it is almost always secondary to pulmonary metastases. Staubitz and associates (1974) reported that

Table VII

Non-seminomatous Testicular Tumours—3-Year Crude Survival Rate (%)

		Histology		
Stage	Author	Embryonal Ca*	Terato Ca†	Combined
A	Blandy, 1976	8/23 (35)	41/46 (89)	49/69 (71)
	Skinner, 1976a	7/10 (70)	31/32 (97)	38/42 (90)
B	Blandy	2/5 (40)	3/7 (43)	5/12 (42)
	Skinner	16/18 (88)	13/18 (72)	29/36 (80)
A+B	Blandy	10/28 (36)	44/53 (83)	54/81 (67)
	Skinner	23/28 (81)	44/50 (88)	67/78 (86)
C	Blandy	0/17 (0)	0/7 (0)	0/24 (0)
	Skinner	5/8 (63)	2/8 (25)	7/16 (44)
All stages	Blandy	10/45 (22)	44/60 (73)	54/105 (51)
	Skinner	28/36 (78)	46/58 (79)	74/94 (79)

* M.T.U. (M.T.A., M.T.I.B.).

† M.T.I. (M.T.I.A.).

Comparison of 3-year crude survival between patients managed with combined modalities of therapy based on lymphadenectomy (Skinner) and patients managed by radiation therapy (Blandy) according to stage and pathology of primary tumour. For ease of comparison all tumours classified as teratocarcinoma by the Friedman and Moore Classification were grouped in the M.T.I. category.

6 of their 45 patients with negative nodes developed pulmonary metastases (13%). Thus, it is our current practice to treat all Stage A patients prophylactically with 2 courses of actinomycin D therapy. If elements of choriocarcinoma are present in the primary tumour, cyclic chemotherapy is continued for 2 years in addition to 1 course of vinblastine sulphate and bleomycin. Staubitz now supports this philosophy and our current results indicate that survival rates can be improved from 82% to 93% in patients who have minimal disease (Table V).

We have demonstrated that 5-year survival now exceeds 90% in patients with negative nodes or minimal retroperitoneal metastases treated by lymph node dissection and chemotherapy, regardless of the primary cell type. In this group, postoperative radiation therapy to the retroperitoneal area offers negligible tumour control, and resultant bone marrow toxicity further decreases patient tolerance to chemotherapy with effective cytotoxic drugs. Table VI illustrates the crude 3-year survival in a collected series of 150 patients with Stage A and B tumours who were treated by surgical dissection without irradiation.

On the other hand, radiation therapy has been a helpful adjuvant in salvaging patients with advanced retroperitoneal metastases. It appears to be most effective in sterilising microscopic residual tumour that may remain after surgical resection of bulky, partially necrotic retroperitoneal masses. It is therefore our policy to consider chemotherapy as the primary adjuvant agent and to reserve radiation therapy for those patients who have extensive retroperitoneal disease following surgical resection. Mediastinal radiation therapy is not given unless mediastinal lymph node metastases are proven at the time of the thoraco-abdominal dissection. A retrospective review of patients treated in this manner has supported this concept and reveals a higher than 80% survival rate in patients with extensive Stage B or C disease treated with a combination of all 3 modalities (Table V).

Patients with Stage C disease or those with clinical evidence of massive retroperitoneal disease continue to require individual assessment. It is important to demonstrate a response to chemotherapy and reduce tumour bulk before embarking on aggressive ablative therapy. If this approach is not considered, extensive retroperitoneal disease may be unresectable at surgical exploration and cure or long-term survival is dependent on removal of bulk retroperitoneal disease.

Table VII represents an attempted comparison between our results and those reported by Blandy (1976). The series are similar in size and suggest that our aggressive approach based on surgical resection with judicious use of combined adjuvant therapy can improve the plight of patients afflicted by these tumours when compared to single modality treatment with radiation therapy.

Summary

Experience in the management of 146 consecutive patients with non-seminomatous tumours of the testis has led to a plan of management based on retroperitoneal lymph node dissection as the primary treatment modality, with use of adjuvant therapy dependent on pathological findings.

Chemotherapy has proved to be the most important adjuvant with postoperative radiation therapy reserved only for patients with extensive retroperitoneal metastatic disease.

3-year crude survival for patients with all stages of disease was 78% and in those in whom the disease was confined to below the diaphragm the survival rate was 85%.

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The Author

Donald G. Skinner, MD, Associate Professor of Surgery/Urology.

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Bacteriuria after Out-patient Cystoscopy

B. RICHARDS and J. R. G. BASTABLE
York District Hospital, York

(Received 19 April 1977; accepted for publication 1 June 1977)

Urethral instrumentation always carries some risk of infection. The infection rate after out-patient cystoscopy has been studied to try to identify patients in whom there is a special risk of infection; and to see whether the infection rate is influenced by the irrigation solution.

Subjects and Methods

Clean catch mid-stream urine samples were taken before and again 48 to 72 hours after instrumentation from 268 subjects (75 women and 193 men) attending for out-patient cystoscopy under general anaesthesia. A further 18 women and 18 men were excluded from the trial as the initial urine sample was found to be infected.

In 135 patients (37 women and 98 men) the irrigation solution was chlorhexidine 1/5,000; in 133 patients (38 women and 95 men) it was sterile water.

The urine samples were obtained without preliminary cleansing of the genitalia, though the foreskin was retracted in men and the labia were held apart in women. Samples were cooled promptly and examined soon. White cells were counted in an aliquot of unspun urine, and bacterial counting was by a tube dilution technique accurate to 30 organisms/ml.

In addition to the age and sex of the patient, a record was made of any history of urinary tract infection in the past, of the presence of residual urine (on IVU or by an isotope technique), and of the estimated size of the prostate gland.

Instruments were sterilised by pasteurisation (76°C for 10 minutes) or by immersion in 2% gluteraldehyde (Cidex) for 10 minutes. Cystoscopy was carried out under general anaesthetic, with the surgeon gowned and gloved. After preliminary skin sterilisation with chlorhexidine in 70% spirit the urethra was irrigated with a 1/5,000 chlorhexidine solution and the instrument was passed, lubricated with glycerine. About 100 ml of irrigation fluid was left in the bladder at the end of the procedure.

Results

Cystoscopy induced an infection (bacteriuria 10^5/ml and at least 10 pus cells/cmm) in 12 of the 268 subjects (4·5%). The infection rate was higher in women than men ($0{\cdot}02 > P > 0{\cdot}01$). The difference in infection rates between subjects having chlorhexidine and those having water irrigation was not significant, taking the group as a whole (Table I).

When urinary infection was not a primary diagnosis the infection rates were lower (Table II). It can be seen that there was no infection in any of the 106 cases who did not have an infective

Table I

The Infection Rate after Cystoscopy: All Patients

	Women		Men		Total	
Chlorhexidine	2/37	5·4%	1/98	1·0%	3/135	2·2%
Water	5/38	13·2%	4/95	4·2%	9/133	6·8%
Totals	7/75	9·3%	5/193	2·6%	12/268	4·5%

Table II

Infection Rate after Cystoscopy: Patients with no Previous Infections

	Women	Men	Total
Chlorhexidine	0/20	0/86	0/106
Water	3/24 12·5%	4/83 4·8%	7/107 6·5%
Totals	3/44 6·8%	4/169 2·4%	7/213 3·3%

Table III

The Infection Rate after Cystoscopy: Patients with History of Previous Urinary Infection

	Women	Men	Total
Chlorhexidine	2/17 11·8%	1/12 8·5%	3/29 10 3%
Water	2/14 14·3%	0/12	2/26 7·7%
Totals	4/31 12·9%	1/24 4·2%	5/55 9·1%

history when chlorhexidine was used as the irrigant; but that 7 of 107 such cases irrigated with water became infected. This difference is significant ($0{\cdot}05 > P > 0{\cdot}02$).

Bacteriuria was noted particularly often after cystoscopies on patients with a history of previous urinary tract infection, even though the urine samples taken immediately before cystoscopy were sterile (Table III). The numbers were small and no difference between infection rates after chlorhexidine or water irrigation was apparent, nor was there a significant difference between infection rates in men and women in this group.

As would be expected, the infection rates were a little higher if cases with bacteriuria 10^5/ml but fewer than 10 pus cells/cmm were counted as infected. Once again, taking all cases together, the women were infected more often than the men ($P < 0{\cdot}001$). Chlorhexidine irrigation was associated with a lower infection rate in the group not having a history of previous urinary tract infection ($0{\cdot}05 > P > 0{\cdot}02$). In those who did give a history of previous infection chlorhexidine did not reduce the incidence of post cystoscopy bacteriuria.

No correlation was found between the infection rate and age, in either chlorhexidine or water irrigation groups. A tendency to a higher infection rate over the age of 50 was not statistically significant.

The infection rates were no higher when residual urine was evident on the IVU (1/39) than in the remaining subjects (11/229). The estimated size of the prostate also had no influence on the infection rate (Table IV).

Positive findings were:—

1. The infection rate in cases who did not have a history of previous urinary infection was higher after cystoscopy with water irrigation than with chlorhexidine.
2. The infection rate was higher in women than in men.
3. The infection rate in subjects having infective disease as a primary diagnosis was higher than those cystoscoped for other reasons, but not significantly so. Although chlorhexidine irrigation appeared to protect against post-cystoscopy infection in patients giving no history of previous infection it did not do so if there was such a history.

Table IV

The Infection Rate after Cystoscopy: Influence of Prostatic Size

	Previous prostatectomy	Normal prostate	Slight enlargement of prostate	Moderate enlargement of prostate	Very large prostate
Chlorhexidine	0/15	0/31	0/31	0/11	0/6
Water	1/12	1/27	1/28	1/23	0/5
Total	1/27	1/58	2/59	1/34	0/11

Discussion

The same technique was used in each of the 268 cases in our series, and bacteriological counting was by a very accurate method. We feel that the high infection rate was unlikely to be due to cross-infection as the infected cases were sporadic, and the infecting organisms differed.

Despite care with asepsis, our infection rate was embarrassingly high (4·3% when all cases are taken together). It is worth noting that there were no infections at all in the 106 cases with no history of previous urinary tract infection who were irrigated with chlorhexidine.

Other studies have shown that the rate of bladder infection after urethral instrumentation differs in different groups. Most investigators have found lower infection rates in the predominantly male urological cases (Lytton, 1961; Higgins, 1966) than in the exclusively female obstetric ones (Slade and Linton, 1960; Brumfitt, Davies and Rosser, 1961; Kaye, de Vries and MacFarlane, 1962). We have confirmed the difference in infection rates between men and women and have found also, not surprisingly, that more women (31/75) than men (24/193) gave a history of previous infection. However, 'the reduction in post-cystoscopy bacteriuria associated with chlorhexidine irrigation in patients with no history of previous infections was equal in both sexes.

The criteria of infection were not critical in our series. We accepted a bacterial count of 10^5 per millilitre together with more than 10 pus cells per cubic millimetre as indicating infection. But the results would not have been materially different if a figure of 10^3 organisms per millilitre had been accepted. In only 7 of our cases were organisms present in concentrations between 10^3 and 10^5/ml, and in only one of these were there more than 10 pus cells/cmm.

Brumfitt *et al.* (1961) have commented that many patients found to have bacteriuria after the passage of a catheter were completely symptom free; and a similar observation was made by Thomlinson, Williams and Cope (1968) who also noted that many of the infected bladders spontaneously cleared themselves, becoming sterile by 6 weeks following surgery. Our experience, like that of Higgins (1966), is similar. Most of the subjects who were bacteriuric at 48 to 72 hours after cystoscopy were asymptomatic.

The bladder is, normally, able to sterilise itself (Cox and Hinman, 1961). It would be expected that abnormalities such as increased residual urine would make infection likely to become established after cystoscopy (O'Grady and Cattell, 1966; Shand *et al.*, 1970). Surprisingly, we found no evidence that an enlarged prostate or the presence of residual urine were associated with a greater likelihood of infection.

It is evident that chlorhexidine, while being a satisfactory irrigation solution for most subjects, did not reduce the rate of post-cystoscopy bacteriuria in patients with an infective history. Perhaps some other prophylaxis is necessary when "infective" subjects are to be cystoscoped.

Summary

The presence of bacteriuria 48–72 hours after cystoscopy has been correlated with the sex and

previous history of the patient, and with the use of chlorhexidine 1/5,000 and water as alternative irrigant solutions.

The infection rate was higher in women than in men. Chlorhexidine in the irrigant solution protected against postoperative bacteriuria in patients who did not have a history of previous urinary infection, but did not do so where there was such history.

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The Authors

B. Richards, MD, FRCS, Consultant Urologist.
J. R. G. Bastable, ChM, FRCS, Consultant Urologist.

Requests for reprints should be made to Mr J. R. G. Bastable, Consultant Urologist, York District Hospital, Wigginton Road, York.

British Association of Urological Surgeons 1978 Annual Meeting

The 1978 annual meeting of the British Association of Urological Surgeons will be held at the Metropole Hotel, Brighton, from 21st to 23rd June inclusive. Those wishing to present a paper or a film should submit an abstract on A4 paper, 25 copies, to the Honorary Secretary, The British Association of Urological Surgeons, at The Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN, not later than 1st December 1977.

Mr Norman M. Matheson

Mr Norman Matheson, who was an Assistant Editor of the *Journal* from 1949 to 1962, died on 27th July 1977.

During his term of office Mr Matheson organised the section on Abstracts from Current Urological Literature and acted as Secretary to the Editorial Committee.

The valuable work he did for the *Journal* was greatly appreciated, not only by his colleagues on the Committee, but also by urologists at home and abroad.

Conferences and Courses

Association of Urological Surgeons in Training

At the annual meeting of the British Association of Urological Surgeons held in Aberdeen in June 1977, an Association of Urological Surgeons in Training was formed. This Association consists of Senior Registrars who are at present in approved training posts in Urology and will be linked to the Association of Surgeons in Training.

A Committee was elected and one member of this Committee will sit on the British Association of Urological Surgeons Council. The Committee would like to hear from any full-time registrar, research worker or lecturer in Urology who would be interested in joining this Association.

For further details of the aims of this Association, please write to one of the following members of the Committee:

D. Arkell, Walsgrave Hospital, Coventry; G. Carswell, Western General Hospital, Edinburgh; M. Dunn, Southmead Hospital, Bristol; D. Tolley, St James's Hospital, Leeds; H. Whitfield, St Bartholomew's Hospital, London; G. Williams, Hammersmith Hospital, London.

1st International Kidney Transplant Course

The 1st International Kidney Transplant Course will take place in Barcelona, Spain, on 24th, 25th and 26th April 1978. This course is organised by the Department of Urology, the Renal Transplant Unit and the Department of Immunology of the "Hospital Clinico y Provincial".

The Directors are Professor J. Ma. Gil-Verent and Drs A. Caralps and J. Vives. Subjects of great interest for urologists, nephrologists and immunologists will be discussed and kidney transplant operations will be carried out and transmitted by television. Those who attend the course may, if they so wish, practice immunology techniques.

For further information write to Dr J. Masramon, Department of Urology, C/ Casanova, 143, Barcelona, Spain.

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Book Reviews

Current Operative Urology. First Edition. E. DOUGLAS WHITEHEAD. Pp. 1250 with 945 illustrations. Hagerstown, Md.: Harper & Row, 1975. $70.00.

The title of this book is misleading. It is not a textbook of operative surgery although most aspects of urology are reviewed. A total of 62 operative procedures or problems are discussed in a most unusual manner. Each topic is introduced by reproducing one or more papers published in the urological literature, and selected by a commentator as being particularly valuable expositions of the subject under discussion. These are followed by a commentary on the content of the papers, with the addition of the personal views of the commentator. Occasionally, an overview is added in particularly controversial areas.

The result is a book of particular interest for the "browser" and one which will inevitably provoke thought and discussion. The trainee surgeon will need a formal textbook of surgery to guide him, but he will find *Current Operative Urology* an invaluable companion with which to widen his horizons. This is a valuable addition to urological literature and one which should be available to every urologist.

D. M. E.

Human Semen and Fertility Regulation in Men. Edited by E. S. E. HAFEZ. Pp. 616 with 559 illustrations. St Louis: Mosby, 1976. $47.50

This book might be described as an introduction to andrology, but not in the sense of being a beginners' guide; it is a presentation of the extent of the subject to those who need to be convinced that andrology is as worthy of being a specialty as gynaecology.

Of the 98 authors of the 56 chapters, only 9 have even a Urology Department address.

The 56 chapters are grouped into sections—functional anatomy, biology of spermatozoa, biochemical andrology, functional biochemistry of proteinases and inhibitors, immuno-andrology, clinical andrology, behavioural and psychiatric andrology, and fertility regulation in men. Finally there are 10 brief appendices of notes on laboratory techniques. Most of the chapters are written by more than one author, though this is not obvious to the reader.

The clinical urologist will find some of the biochemistry above his head, and some beyond his interest, but also he is sure to find many fascinating facts. Most of these are of no obvious immediate value except to help him to appreciate the complexity of the subject—and to understand why the results of treatment are so unpredictable.

He will be much more at home in the chapters on clinical aspects of male infertility and mechanical disorders of the genital tract. These have comprehensive reviews of their subjects with usually reasonable analytical comments.

The final chapters—on fertility control—range from vasectomy to sperm enzyme inhibitors with correspondingly variable urological interest.

The book is beautifully produced with numerous clear line drawings and a number of electron microphotographs.

This book should at least be seen by anyone involved in the management of male infertility—and owned by every infertility clinic.

W. K. Y.

Male Infertility: Workup, Treatment and Research. Edited by A. J. K. COCKETT and R. L. URRY. Pp. xii+328. New York: Grune and Stratton, 1977. £10·30.

This book is a report on the Proceedings of the Symposium held at the University of Rochester, New York, in April 1976, and comprises the presentation of papers and verbatim records of the discussions.

It is really an updating of knowledge of the facets usually presented in symposia on male infertility—reproductive physiology, endocrine aspects, sperm antibodies, varicocele, etc.

Although those who have kept up to date with the literature will find little new in this book, it is an excellent summary of the present state of knowledge in the clinical aspects of male infertility, and has very adequate lists of references.

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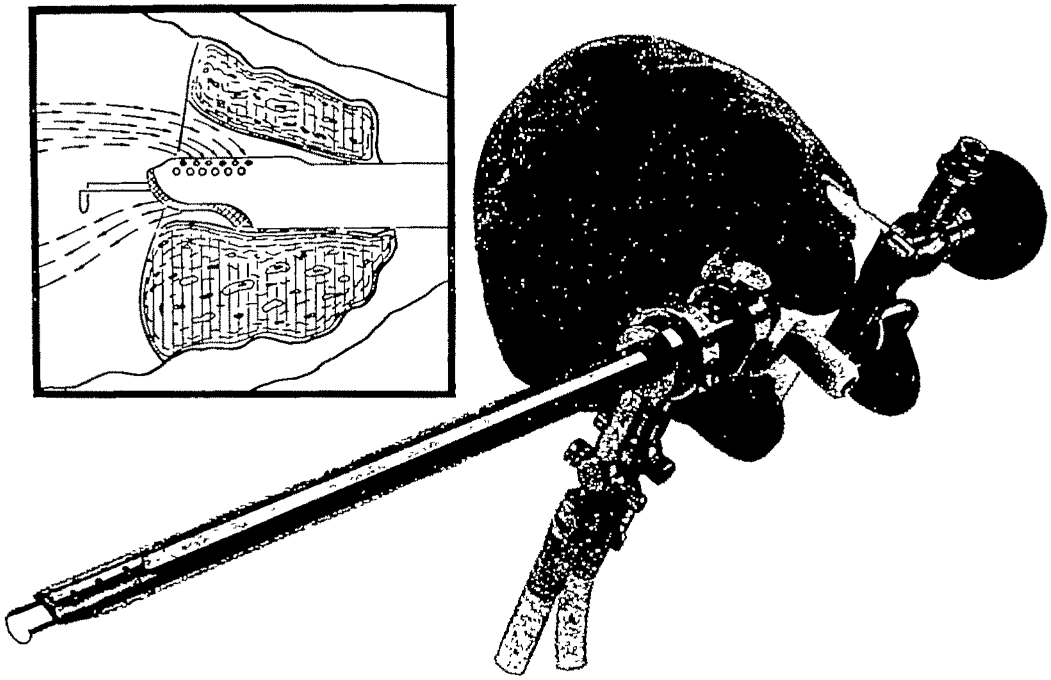

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Old Units			Conversion factor Multiply by:		S.I. Units	
Constituent	Normal range	Units	Old to New	New to Old	Normal range	Units
Venous Blood						
Albumin	3·5–5·5	g/100 ml	10	0·1	35–55	g/l
Bicarbonate (total)	24–30	mEq/l	1	1	24–30	mmol/l
Bilirubin	0·1–0·8	mg/100 ml	17	0·059	2–14	μmol/l
Calcium	8·6–10·5	mg/100 ml	0·25	4	2·15–2·65	mmol/l
Chloride	100–107	mEq/l	1	1	100–107	mmol/l
Cholesterol	140–240	mg/100 ml	0·026	38·5	4·0–6·5	mmol/l
Creatinine	0·6–1·4	mg/100 ml	88	0·0114	55–125	μmol/l
Glucose	65–95	mg/100 ml	0·056	18	3·5–5·5	mmol/l
Iron	110–130	μg/100 ml	0·18	5·6	circa 20	μmol/l
Magnesium	1·4–1·8	mEq/l	0·5	2	0·70–0·90	mmol/l
Phosphate	2·5–4·5	mg/100 ml	0·32	3·1	0·8–1·4	mmol/l
Potassium	3·8–5·2	mEq/l	1	1	3·8–5·2	mmol/l
Protein (total)	6·5–8·0	g/100 ml	10	0·1	65–80	g/l
P.B.I.	3·75–7·5	μg/100 ml	79	0·0127	300–600	nmol/l
IgG	500–1600	mg/100 ml	0·01	100	5·0–16·0	g/l
IgA	125–425	mg/100 ml	0·01	100	1·25–4·25	g/l
IgM	50–180	mg/100 ml	0·01	100	0·5–1·8	g/l
Sodium	136–149	mEq/l	1	1	136–149	mmol/l
Transferrin	150–300	mg/100 ml	0·01	100	1·5–3·0	g/l
Triglyceride	60–140	mg/100 ml	0·0113	88·5	M2·0 P<1·5	mmol/l
Uric Acid	2–7	mg/100 ml	0·06	16·7	0·1–0·4	mmol/l
Urea	15–40	mg/100 ml	0·17	6·0	2·5–6·5	mmol/l
Arterial Blood						
Base Excess	−3–+3	mEq/l	1	1	−3–+3	mmol/l
PCO_2	32–46	mm Hg	0·135	7·5	4·5–6·0	kPa
PO_2	80–100	mm Hg	0·133	7·5	10·5–13·5	kPa
Urine Outputs/24 hr						
Calcium	200	mg	0·025	40	5	mmol
Creatinine	1–2	g	8·8	0·113	9–18	mmol
5H1AA	3–17	mg	5·23	0·19	16–90	μmol
Inorganic P.	1000	mg	0·032	31	30	mmol
Magnesium	100	mg	0·041	24	4·2	mmol
Potassium	70	mEq	1	1	70	mmol
Protein	<0·05	g	1	1	<0·05	g
Sodium	200	mEq	1	1	200	mmol
Urea	25	g	17	0·06	400	mmol
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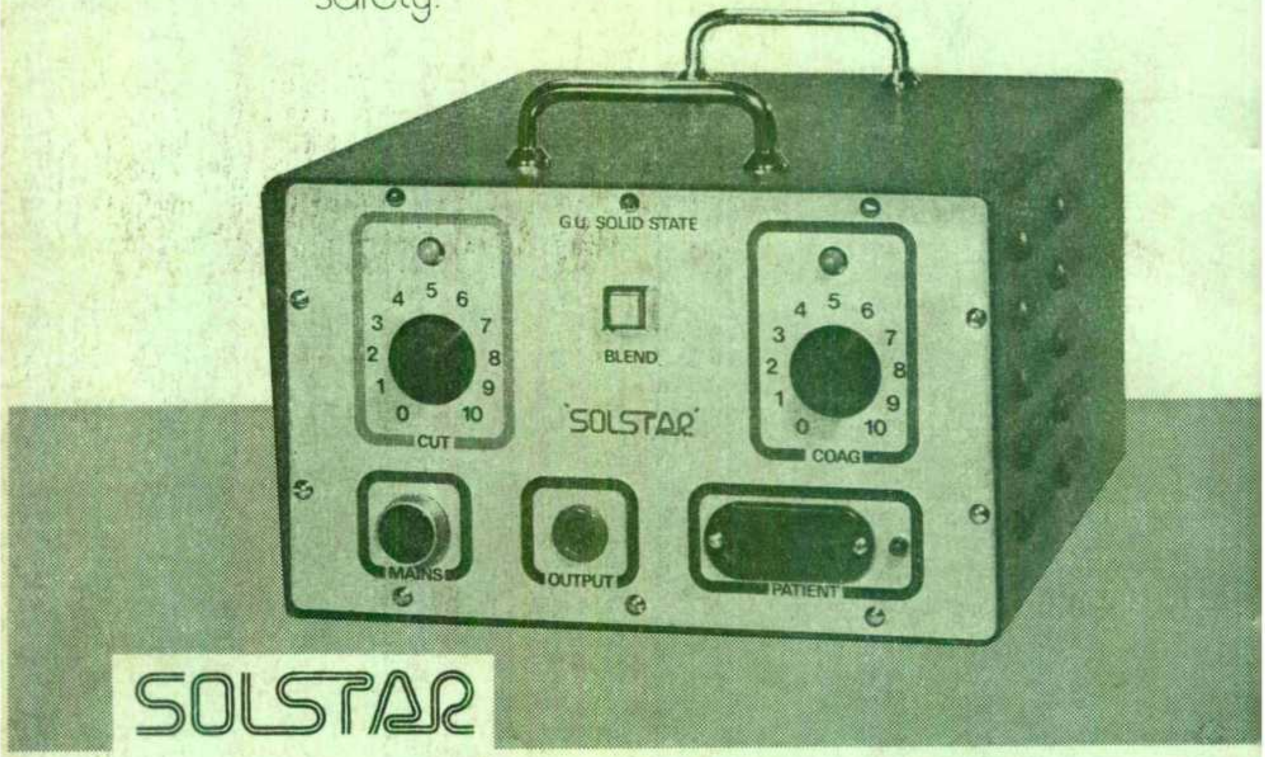

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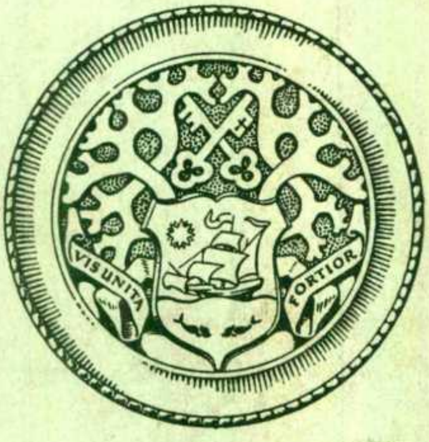

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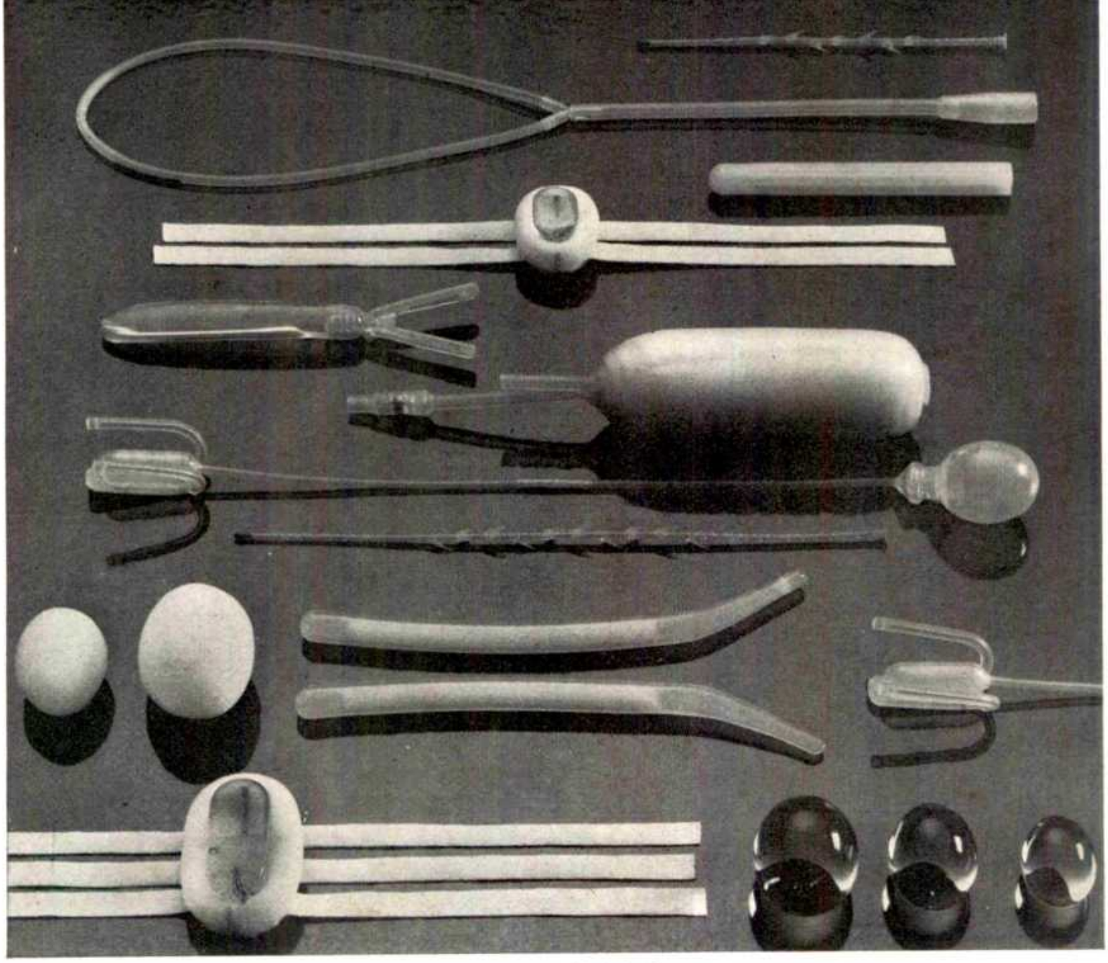

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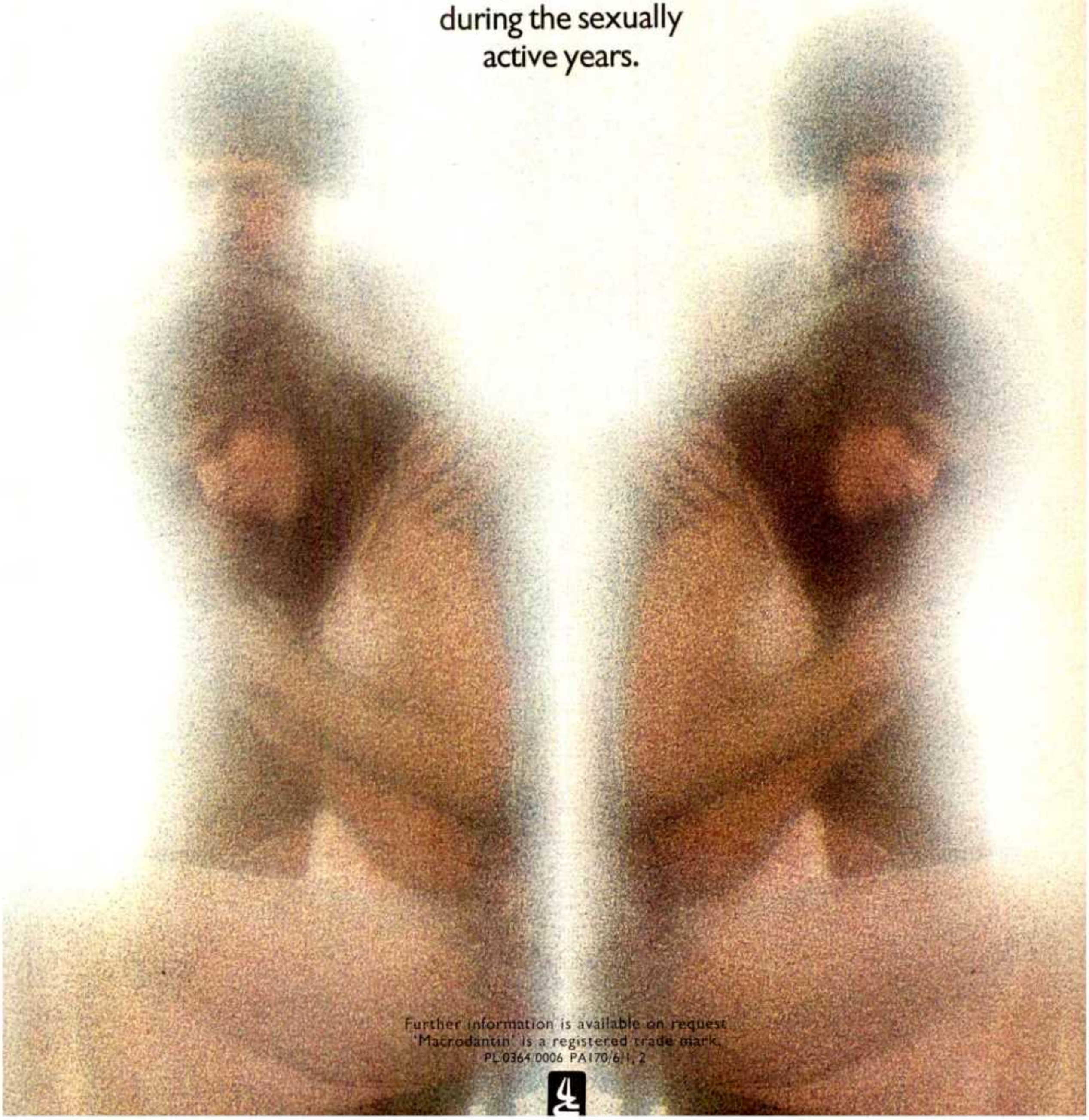

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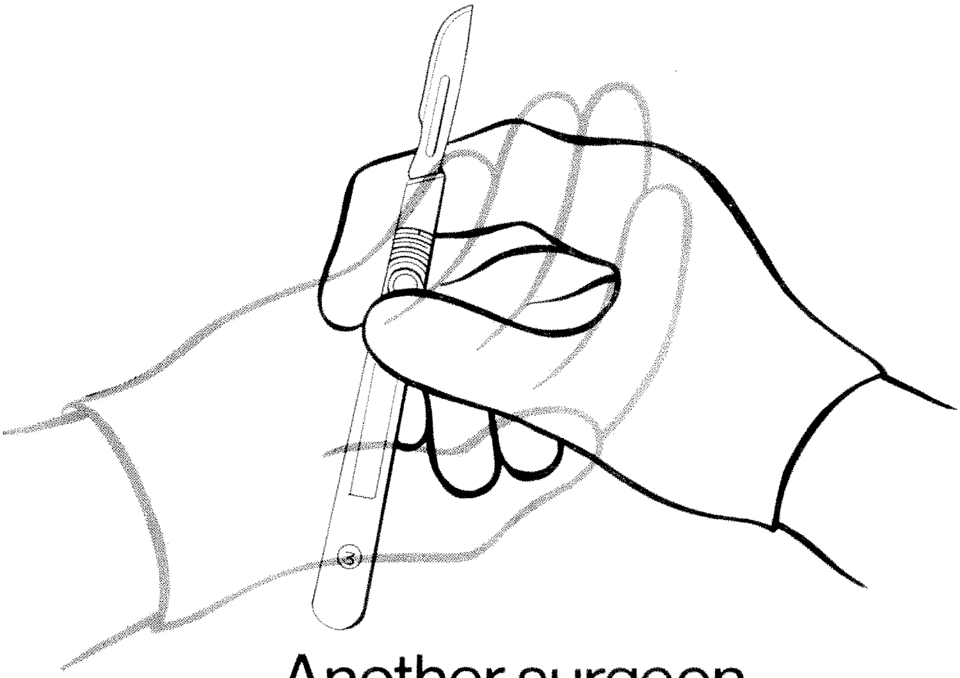

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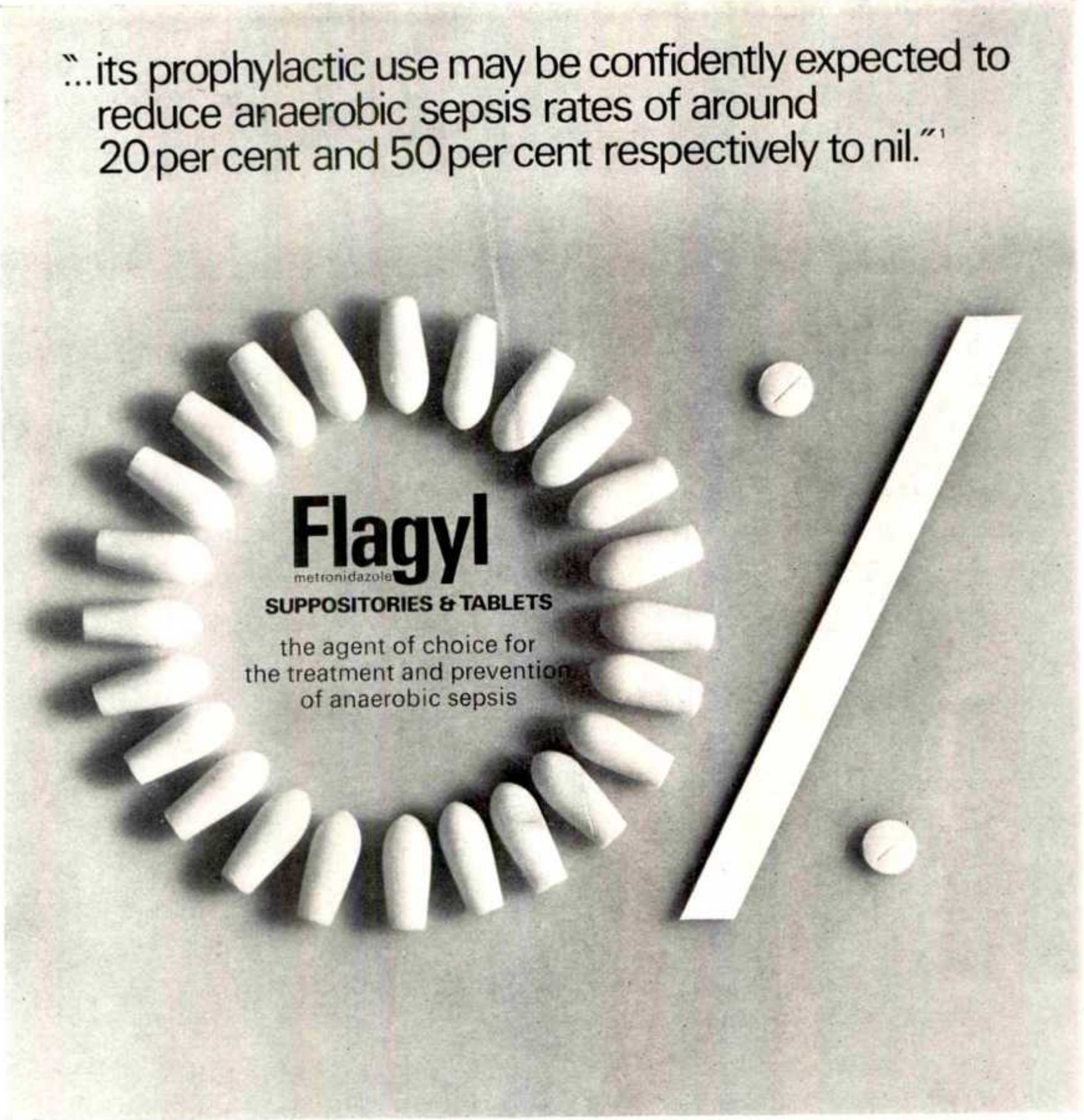
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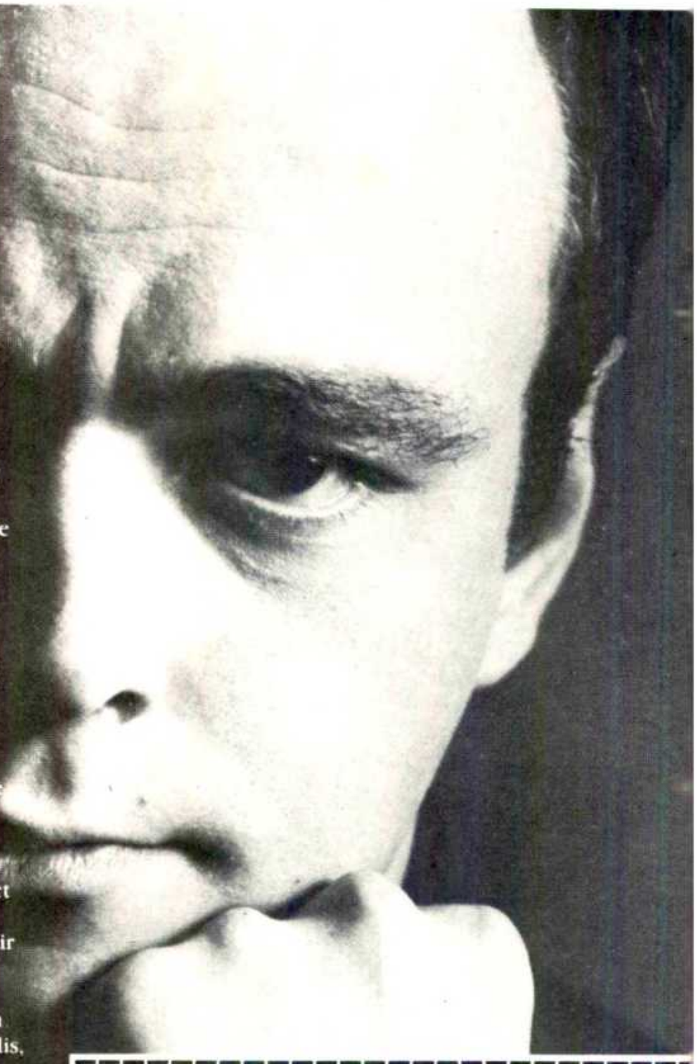

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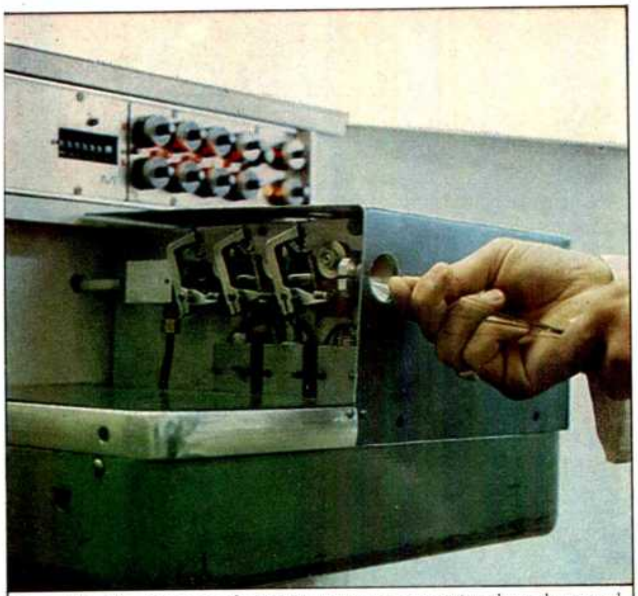

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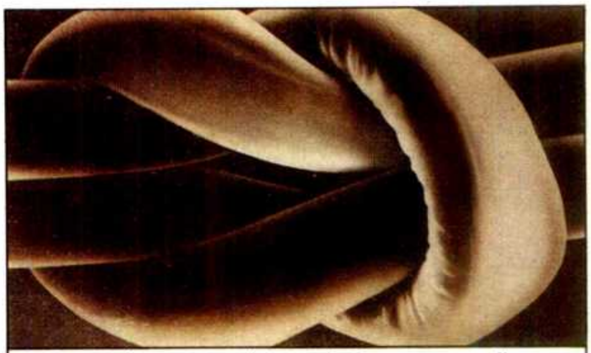

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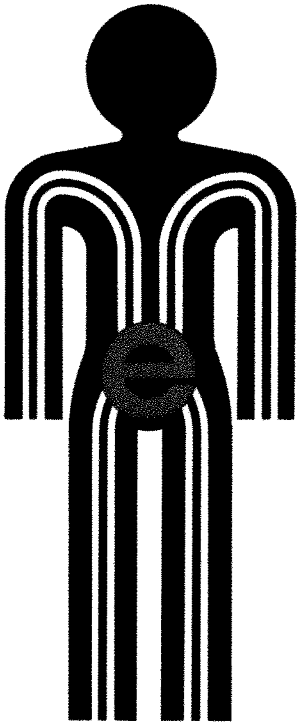

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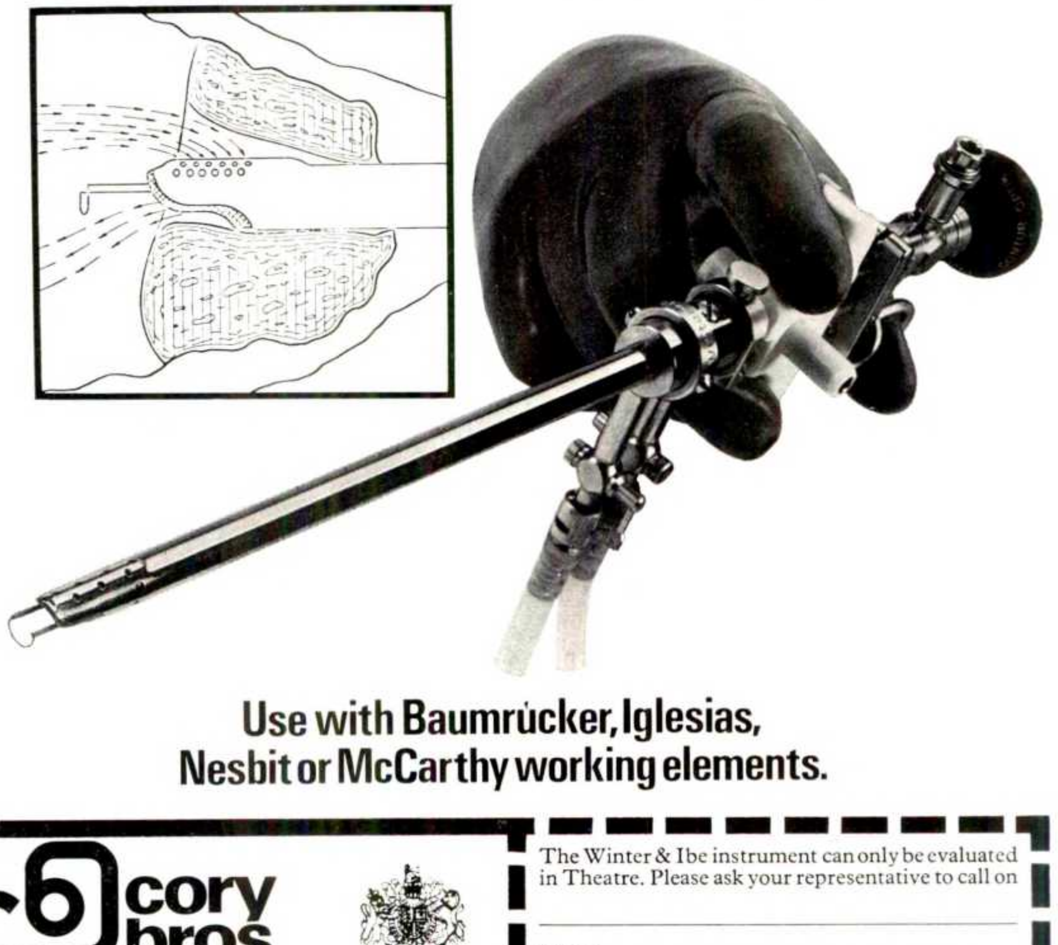

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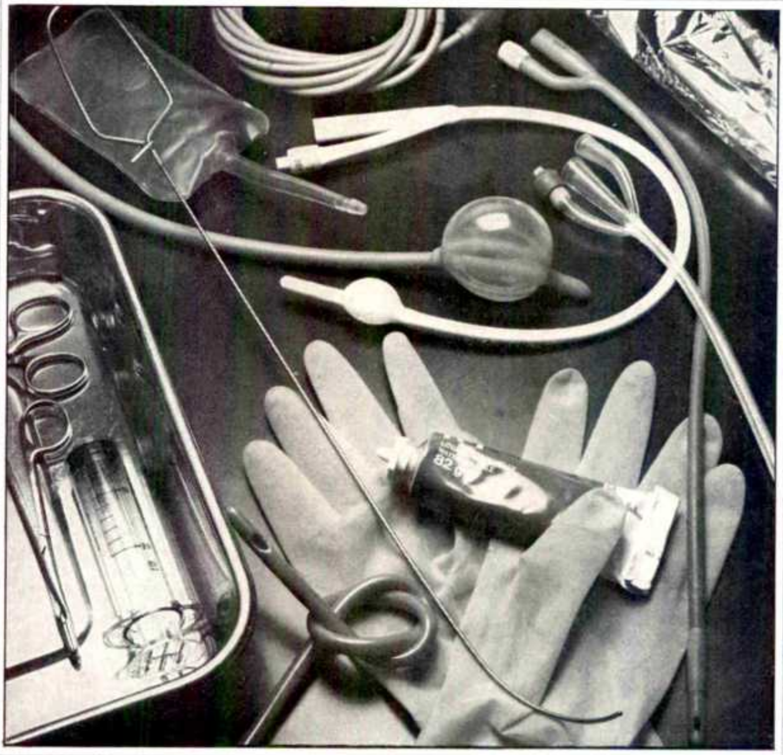

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The Modified Makari Skin Test in Urology—Is it Significant?

K. W. MUNSON and D. E. H. TEE
King's College Hospital, London

The Makari skin test is an *in-vivo* technique designed to detect the presence of cancer. It is not specific for any particular cancer or target organ. It is based on work by Makari who, by using the Schultz-Dale technique of the sensitised guinea-pig uterus, reported the existence of tumour-specific antigens and antibodies in the serum of patients with malignant disease (Makari, 1955, 1958). He subsequently found these antigens to be of a polysaccharidal nature and this has been supported by Smith (1963) and Jeanloz (1970). Because the Schultz-Dale technique is not suitable for general testing, Makari developed an intradermal test using polysaccharidal antigens derived from human carcinoma, sarcoma and lymphoma. These antigens, when injected intradermally, gave an immediate erythematous reaction which is potentiated when the antigens are preincubated with the patient's serum. A positive result consists of an erythematous reaction to any one of the antigens whose mean diameter compared to that given by a control injection without antigen is greater than 1·35. The test gave positive results in many patients with early carcinoma and in a

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Table I

Delayed Hypersensitivity Skin Testing

Antigen	Dilution	Criteria of positive reaction
Tuberculin	1 : 10,000	Induration, 1 cm or greater
Candida	1 : 1,000	
Trichophytin	1 : 20	
Streptokinase/Streptodornase (Varidase)	1 : 20	Induration, 2 cm or greater

(0·1 ml Intradermal injections—forearm. Read—48 hours)

Table II

Patients with Primary and Recurrent Malignancy

	Primary		Recurrent	
Makari test:	Positive	Negative	Positive	Negative
All patients	59	31	89	78
Excluding known anergic patients	59 (96%)	2	89 (81%)	21

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

lower proportion of patients with metastases. The test was positive in tumours from a wide variety of organs and also in a group of reactive and inflammatory disorders including diverticulitis and peptic ulcer. Recent modification of the test, by purification of these antigens and by preabsorption of the patient's serum, has considerably improved the results as compared to those of the unmodified test (Tee, 1976).

Methods

A double-blind study was undertaken to determine the role of the modified Makari skin test as a diagnostic aid, in monitoring primary treatment, in the detection of early recurrence, and as a guide to prognosis. Patients with either a known or suspected diagnosis of a urological cancer were asked to undergo the test and their consent was obtained. The administrator of the test was unaware of the diagnosis as the test was performed preoperatively and also the injections were randomly coded so that the sites of the control injections were not known.

Disease Status

Diagnosis and staging of carcinoma was made by histological examination of tissue when available but otherwise by clinical and operative assessment of the patient.

Table III

Distribution by Stage of Disease of 249 Patients with Primary and Recurrent Malignancy

		Makari negative	
	Makari positive	"Anergic"	Not tested for anergy
Stage I (non-invasive)	115	35	4
Stage II	15	23	6
Stage III	8	8	6
Stage IV	10	12	7
Totals	148	78	23

Table IV

Distribution by Stage of Disease of 90 Patients with Primary Tumours

	Makari positive	Makari negative
Stage I (non-invasive)	42	8
Stage II	9	23
Stage III	4	
Stage IV	4	
Totals	59	31

Bladder, 72; Kidney, 12; Prostate, 2; Testicle, 3; Penis, 1.

Detection of Anergy

When tumour was present, confirmed either histologically or clinically, in the presence of a negative Makari test, delayed hypersensitivity skin testing was performed. Patients were injected with 4 recall antigens, rather than 1, to increase the chance of detecting prior exposure and sensitisation. The patient was judged to be "anergic" when negative responses were obtained with all 4 antigens (Table I) and in such cases the Makari test could not be taken to indicate the tumour status.

Results

1. Diagnosis

The results of 90 patients with primary tumours and 167 patients with recurrent tumours are presented. Of those patients with primary tumours, 59 gave a positive result and 31 a negative result. Of the 31, 29 were tested for and found to be anergic; and excluding these anergic patients, the test was positive in 96% of this group. Of 167 patients with recurrent malignancy, 89 gave a positive result and 78 a negative result. Similarly, of the 78, 57 were tested for and found to be anergic and excluding these, the test was positive in 81% of the remainder (Table II). Makari originally claimed that the test was positive in early rather than late stage disease and Table III shows the distribution of patients by their stage of disease. Of the 148 with a positive result, 115 (78%) were stage I non-invasive disease compared to 101 with a negative result in whom only 39 (39%) had stage I disease.

Table IV shows similar findings in the 90 patients with primary tumours, *i.e.* 71% with a positive result having stage I disease as opposed to only 25% stage I disease in the negative group.

Table V

Follow-up Tests on Primary Tumours

Initial test:	Makari positive (59)			
Follow-up test:	Remaining positive (8)		Converting to negative (25)	
	Tumour present	Tumour absent	Tumour present	Tumour absent
	6	2	3*	22
Number still to be followed up	26			

* Anergic—post-radiotherapy.

Table VI

Patients with Non-Malignant Disease

Total	112
Excluding 5 who developed suspect or proven cancer	107
Makari negative	71 (66%)
Makari positive	36 (34%)

Table VII

Scrotal Masses

Preoperative diagnosis:	*? Tumour* 14	
		Treatment
Makari positive	4 (1)	4 Orchidectomy for tumour
Makari negative	10 (1)*	5 Orchidectomy for benign disease apart from*
		5 Explored
Preoperative diagnosis:	*Benign disease* 4	
Makari positive	0	
Makari negative	4	

*Anergic patient with recurrent semminoma after radiotherapy.

2. *Monitoring Primary Treatment*

The results of 33 follow-up tests on patients with primary tumours have shown that 8 remained positive after treatment, 6 of whom had residual tumour present, whilst in the other 2 there was no evidence of tumour. Of the 25 who converted to a negative reaction after primary treatment, 3 had tumour present. All of these had radiotherapy as their primary treatment and all were found to be anergic on repeat testing. In the remaining 22, no evidence of residual tumour was found. (Table 5).

3. *Control Patients*

Out of a total of 112 patients, 5 have been excluded from the category of non-malignant disease, leaving a total of 107; of whom 36 (34%) gave a positive reaction (Table VI).

Discussion

The results of this study suggest that the test will be useful in certain clinical situations. Diagnostically it may help in differentiating between benign and malignant renal and scrotal swellings. The results from this study of patients admitted with a scrotal mass have been analysed and are shown in Table VII. In 14 patients with a preoperative diagnosis of tumour, the Makari test was able to detect those patients who had non-malignant disease, apart from one patient with anergy. The results from this small group are encouraging and the test appears to be of value in preventing unnecessary orchidectomy. Our results in patients with renal lesions are also encouraging although the incidence of anergy in this group is much higher.

The test appears to be able to detect whether primary treatment has been adequate or not, the persistence of a positive reaction indicating that tumour is still present and conversion to a negative reaction indicating absence of tumour. However, anergic patients must be recognised as the test result in such patients does not concur with their tumour status. With this limitation, it might still be useful in monitoring the treatment of renal and testicular tumours and also be of help in the post-cystectomy situation.

There are 3 possible explanations for the positive result in control groups of patients: (*a*) the presence of an occult primary as yet clinically undetectable, (*b*) the presence of a reactive or inflammatory disorder and (*c*) a false positive reaction. This problem will only be resolved by a long-term follow-up of these patients.

Summary

The Makari test is able to detect the presence of cancer in 95% of patients with primary tumours having excluded anergic patients.

The test is useful in monitoring primary treatment.

A long-term follow-up is necessary to determine the reason for patients' unexplained positive reactions in a control group of patients.

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The Authors

K. W. Munson, FRCS, Senior Registrar in Urology.
D. E. H. Tee, FRCPath, Consultant Immunologist.

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Dynamic Scintigraphy in Clinical Urology

P. H. O'REILLY, R. S. LAWSON, R. A. SHIELDS, H. J. TESTA, E. CHARLTON EDWARDS and
R. N. P. CARROLL
Departments of Urology, Nuclear Medicine and Medical Physics, Manchester Royal Infirmary, Manchester

In recent years there have become available a number of techniques involving the use of radioisotopes for the investigation of the patient with genito-urinary problems. Clearance studies and 131 I-hippuran renography are well established and widely used. The development of gamma camera and fast data-processing systems have added a further dimension to the information available from nuclear medicine techniques. This paper describes the technique of dynamic renal scintigraphy and the particular applications which we have found valuable—the evaluation of renal parenchymal lesions and the investigation of renal haemodynamics.

Materials and Methods

The dynamic renal scintigram or scan is performed on the sitting patient in the PA projection. No special preparation is required. A number of radiopharmaceuticals are available, the Technetium-^{99m} agents ^{99m}Tc-DTPA, ^{99m}Tc-Gluconate and ^{99m}Tc-DMSA being the most popular at the present time. All of these are filtered but a proportion of each is retained by chemical combination to the cells of the proximal tubule to varying degrees, allowing pictures of the parenchyma to be obtained.

The first part of the procedure is termed the *vascular* study or isotope angiogram. 10 mCi of the radiopharmaceutical is injected through a Butterfly (Abbott) cannula into a suitable superficial vein and quickly flushed through with 10 ml. of normal saline. This produces a bolus effect, pushing the small amount of high activity through the vascular system to the aorta. Pictures are commenced on the gamma camera (Neclear Enterprises Mk III with Digital Equipment Co. PDP-12 computer or General Electric Radicamera with Med II system) at 5 seconds and collected at 1-second intervals for 50 seconds. At the same time, analogue pictures are obtained at 5-second intervals for 30 seconds. This study allows storage, easy recall and display on the visual display unit of the isotope angiogram. In this way, visualisation and analysis of the passage of the radiopharmaceutical through aorta, renal arteries and kidneys is possible, so detecting abnormal blood flow through tumours, inflammatory lesions and arteriovenous malformations. Avascular areas caused by abscesses, cysts or infarcts and vascular anomalies such as aortic aneurysms, prosthetic grafts, arterial stenoses or renal homografts may also be demonstrated.

Following this study, *parenchymal* pictures can be obtained from 2-minute pictures on the gamma camera-computer system for 10 or 20 minutes or longer, at the same time taking analogue pictures of 400,000 counts at intervals such as 2, 10 and 20 minutes (or later for agents such as ^{99m}Tc-DMSA). Parenchymal morphology and function can then be directly compared with the haemodynamic characteristics and appearances available on the dynamic study.

The technique is simple, rapid, non-toxic and safe and we have encountered no side-effects in over 1,000 such studies.

Results

There are 2 main situations in which renal scanning can be of value to the urologist—renal tumours and renovascular abnormalities.

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

Space-occupying Lesions of the Kidney

Most space-occupying lesions of the kidney are detected by intravenous urography (IVU) but their true nature is not always clear from this investigation. Where grey-scale ultrasound facilities are available this non-invasive study may help in distinguishing cyst from tumour, but it is more common to proceed to arteriography for the preoperative diagnosis. However, the majority of renal carcinoma are vascular tumours and it is possible to exploit this tumour circulation by comparing its characteristics on the isotope angiogram with the appearances on the parenchymal study. Should the latter demonstrate a "cold" space-occupying area which, on the dynamic study, shows a hypervascular blush or "hot" area, then the diagnosis of renal tumour is almost certain (Figs. 1 and 2).

In a prospective study of 67 patients referred for renal scanning with suspected malignancy, 23 were found to have renal tumours, of whom 18 were correctly diagnosed by the isotope scan. 17 of these were hypernephroma and 1 a transitional cell tumour of the renal pelvis. Of the remaining 5 cases, 4 had tumours in non-functioning kidneys (2 hypernephroma, 2 transitional cell tumours) while the 5th was a diffuse tubular cell carcinoma which showed uptake of tracer and no evidence of a cold area. Uptake of tracer by renal tumours is extremely rare with only 2 previous recorded cases, 1 being a tubular adenoma taking up ^{197}Hg-chlormerodrin (Caplan *et al.*, 1968) and the other a renal carcinoma taking up ^{99m}Tc-DMSA (Pion, Staab and Stevens, 1976). Our case showed generalised concentration of ^{99m}Tc-DTPA and represents a false negative result. It is possible that where tubular elements predominate in a tumour, the chemical binding property to the proximal tubular cells is preserved and this appears on the scan as uptake. Nevertheless, this phenomenon is extremely rare.

The majority of cases were hypernephroma in which an 89% success rate was achieved in pre-operative diagnosis by the isotope method. Care must be exercised in non-vascular tumours such as transitional cell lesions (Wright and Walker, 1975; Leong *et al.*, 1976) and tumours with advanced necrotic changes, where there may be no vascular blush. Such cases form a minority of renal tumours, but require arteriography.

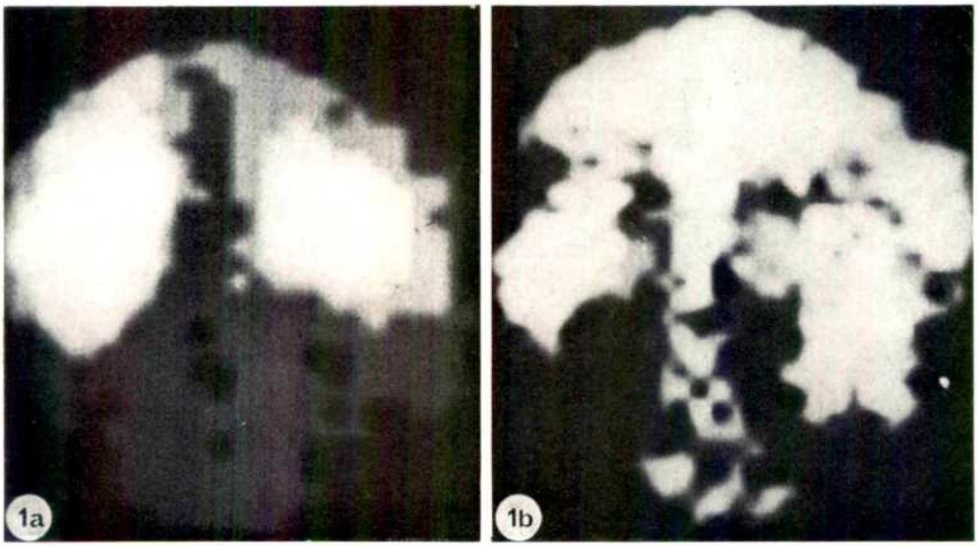

Fig. 1. (*a*) Parenchymal study showing space-occupying lesion at lower pole right kidney. (*b*) Vascular study showing corresponding area to be highly vascular.

There were 20 renal cysts in the series of which 19 were correctly diagnosed on the isotope study. Fig. 3 shows the appearances found in renal cysts where the dynamic angiogram reveals a totally avascular cold lesion corresponding to a cold area on the parenchymal study. These findings are summarised in Table I. Of the remaining cases, 13 have, as yet, no firm diagnosis. Most of these are cases of unexplained haematuria in whom it is unlikely that a positive pathological diagnosis will be found. A renal abscess was accurately diagnosed, but an A-V fistula was below the 2 cm limit of resolution of the isotope technique.

2 patients presented with deformities of their excretion urogram, suggestive of possible malignancy with a cortical hump and apparently disrupted calyces. Scanning in these cases was normal with even tracer uptake and equal vascularisation throughout the kidneys. These were diagnosed as renal pseudotumours and this diagnosis was confirmed at arteriography (Fig. 4). Being normal parenchyma, such pseudotumours exhibit normal uptake of tracer and, accepting the limit of resolution of the procedure, such a normal result in the isotope scan excludes renal carcinoma. The appreciation of this condition will reduce the incidence of needless exploration or nephrectomy, and the scintigram is thus of value in this situation.

Vascular Abnormalities

The correct recognition and assessment of renovascular disease can influence the management of the patient and in this respect the isotope angiogram provides a simple but valuable adjunct to overall evaluation.

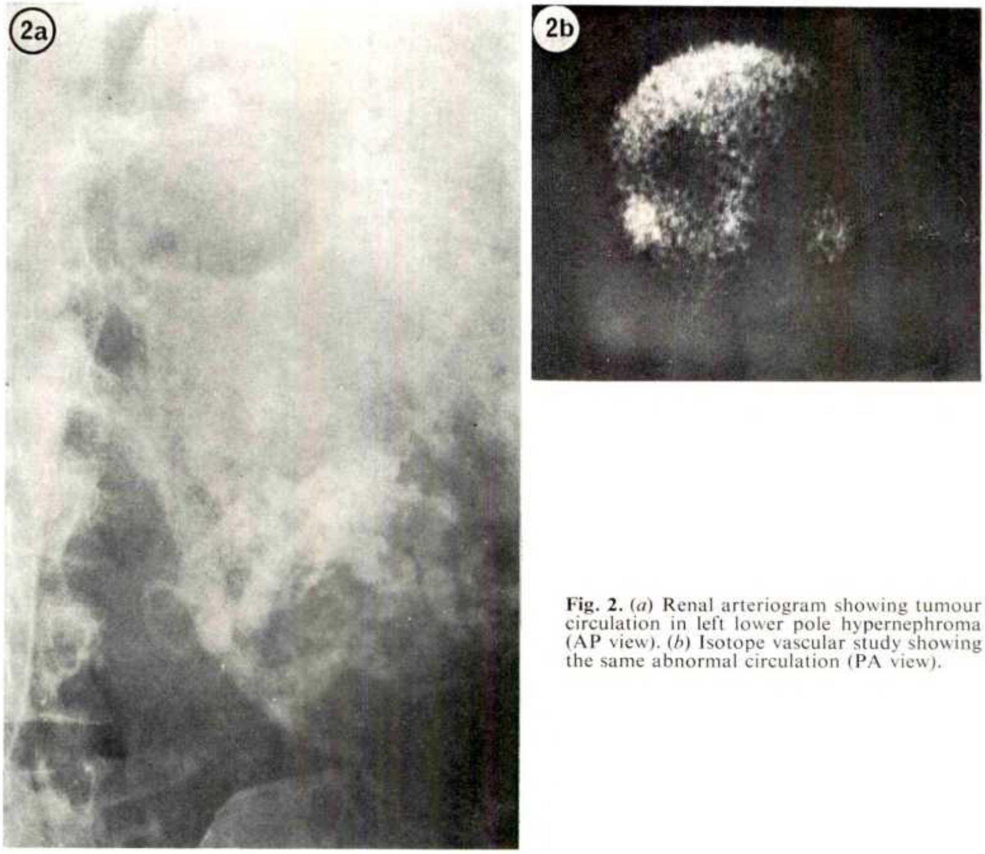

Fig. 2. (*a*) Renal arteriogram showing tumour circulation in left lower pole hypernephroma (AP view). (*b*) Isotope vascular study showing the same abnormal circulation (PA view).

Example 1. A 32-year-old female was admitted with haematuria and loin pain following a trivial episode of trauma to the loin. IVU showed a normal left kidney and a right hydronephrosis. The renal scan suggested compensatory hypertrophy of the left kidney and that the right was not only poorly functioning, but had an impaired blood supply (Fig. 5). At operation the right renal artery was found to be small and contained recent thrombus, probably traumatic in origin and almost completely occluding the lumen. Nephrectomy was performed.

Example 2. A patient with known nephrotic syndrome was referred in a very poor physical condition with a possible diagnosis of unilateral renal vein thrombosis. A dynamic renal scan indicated a good blood supply to the right kidney but a poor flow to the left. Circulation curves were obtained (Fig. 6) from the computer data and vascular mean transit times (MTT) calculated for each kidney. The right MTT was 7·4 seconds—within normal limits—while the left was 58·6 seconds—strongly in favour of renal vein thrombosis. This simple non-invasive test was of considerable help in the management of this seriously ill patient.

Example 3. A patient was investigated for loin pain and found to have a solitary space-occupying lesion in the upper pole of each kidney. Arteriography failed on 2 occasions because of arrest of the catheter with considerable bleeding. A renal scan was performed since the IVU was equivocal as to the aetiology of the renal lesions. The dynamic scan clearly demonstrated the lesions to be avascular cysts, and also showed a large aortic aneurysm at the level of the renal arteries, accounting for the failed arteriogram (Fig. 7).

Estimation of Mean Transit Time

It is possible from the computer-stored data on the first circulation to produce individual circulation curves of the vascular transit of the radiopharmaceutical through aorta and each kidney. These circulation curves take the form shown in Fig. 6 with a rapid uptake and downslope

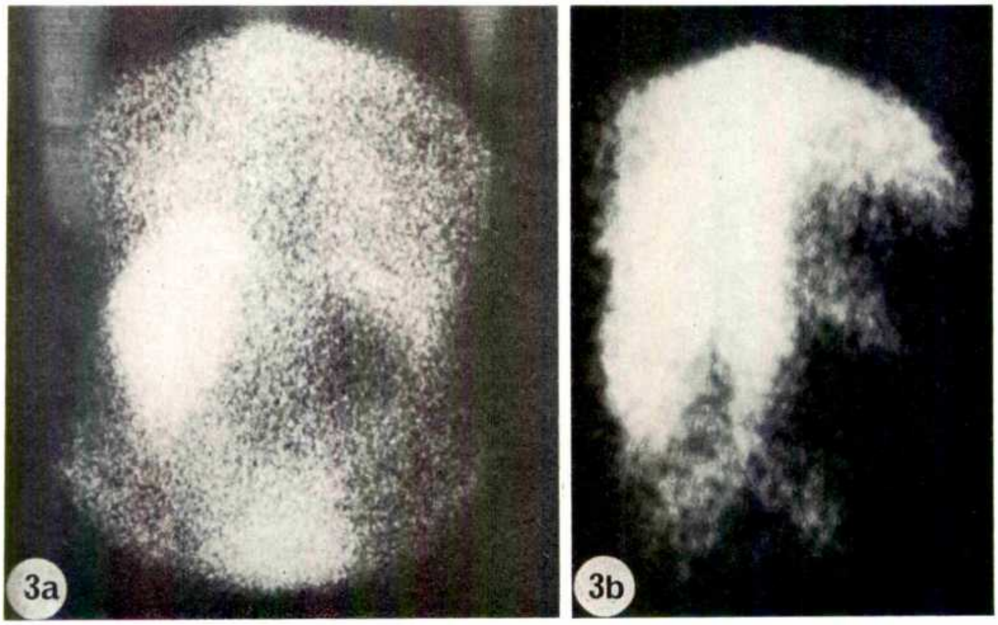

Fig. 3. (*a*) Parenchymal study in case of right renal cyst showing cold area. (*b*) Vascular study in same patient showing lesion to be avascular.

corresponding to the first circulation followed by smaller oscillations due to re-circulation. It is possible to exclude re-circulation by fitting an exponential function to the first downslope and, by applying a mathematical formula to the area under curve, the computer can calculate an index of the mean transit time from the injection site to aorta and each kidney; their difference gives an index for the blood flow through the individual kidneys. While problems exist from background activity and the proximity of splenic and hepatic circulation to the renal images, provided a good bolus injection is given to obtain the vital first downslope to which the exponential must be fitted, and provided liver and spleen do not overlie the kidneys, the technique is accurate.

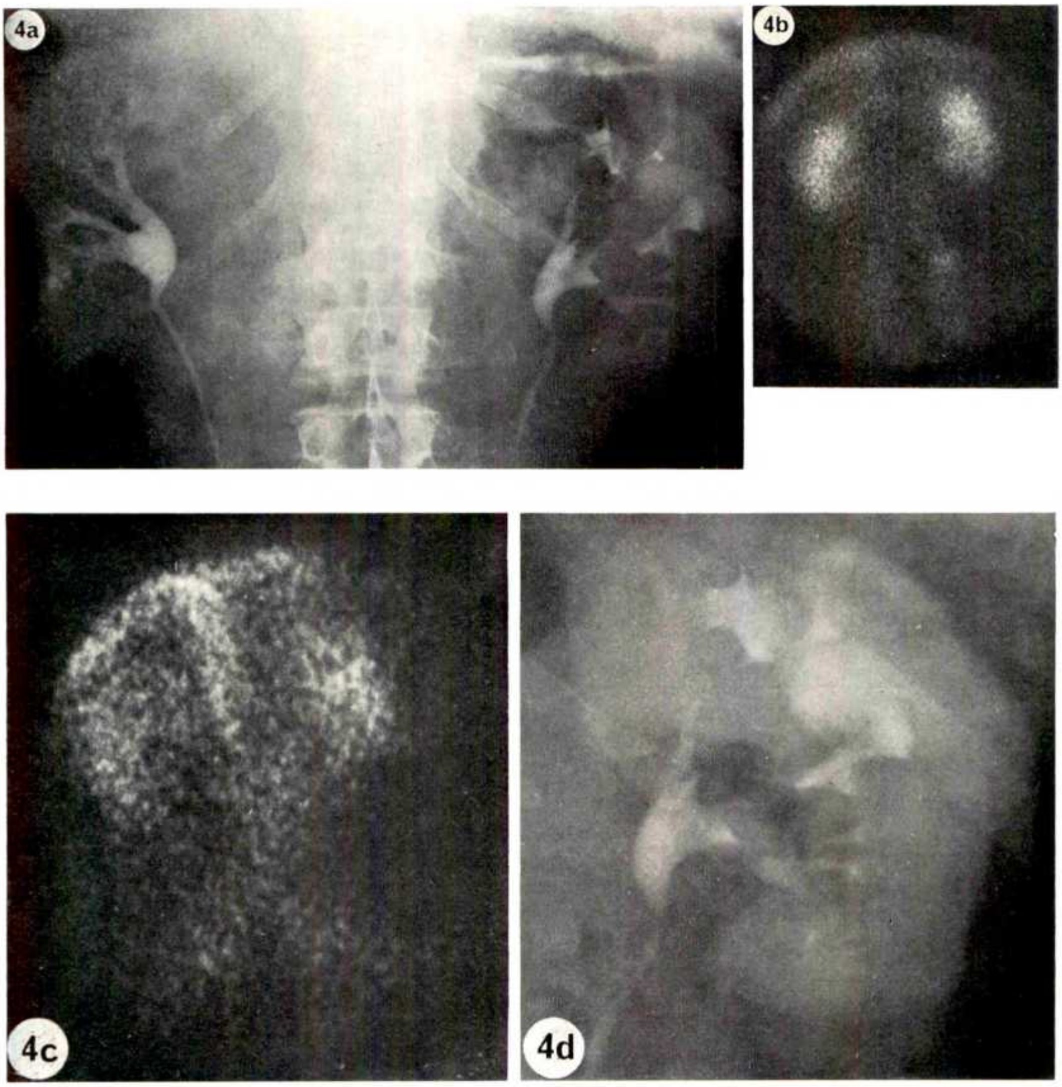

Fig. 4. (*a*) IVU in patient with pseudotumour showing left cortical "hump" and calyceal disruption. (*b*) Isotope parenchymal study showing normal appearances. (*c*) Isotope vascular study showing normal appearances. (*d*) Renal arteriogram confirming the absence of malignancy and diagnosis of pseudotumour.

In a consecutive series of 57 patients presenting with a complaint of loin pain, 9 had no apparent cause for the symptoms after full urological work-up. However, when mean transit times were calculated in 5 cases the MTT was significantly greater on the side of the patients' symptoms than on the other side (Table II). The reason for such a discrepancy is not clear. 3 of the 5 patients fell into the category of loin pain/haematuria syndrome and the possibility of a prolonged transit time consequent on a form of microangiopathy is a hypothesis.

Discussion

The intravenous urogram is accepted as being the primary investigation available to the urologist. Nevertheless, in space-occupying disease it is often equivocal and gives no information on the vascular characteristics of the lesion. This may be true of ultrasound. We believe that before proceeding to arteriography or needle puncture, isotope renal scanning by the methods outlined above can be of considerable value. Its diagnostic accuracy in renal carcinoma is good, as is its ability to identify renal cysts correctly. In avascular tumours such as the advanced necrotic renal carcinoma, nephroblastoma or transitional cell lesion, the scan is almost always abnormal but not diagnostic. However, where the scan is conclusive, as in the majority of cases (84%), the patient is saved arteriography by a simple, non-toxic, non-invasive test. If the result is inconclusive, arteriography can then be performed.

The technique is also valuable in renovascular disease and with the help of data-processing equipment, quantitative individual haemodynamics can be performed. The tests are easily stored and re-called and are easily reproducible at a later date if serial estimations are required.

In addition, the test is of value in the assessment of renal transplants, renal trauma, inflammatory disease and uretero-ureteric reflux (O' Reilly *et al.*). It is also applicable to paediatric problems.

Radio-isotope studies are becoming more sophisticated and widely performed in this country and are recommended in the evaluation of urological problems before proceeding to more invasive procedures.

Table I

Patients with Suspected Malignancy investigated by Isotope Renal Scanning

Diagnosis		Scan correct
Renal carcinoma	23	18
Hypernephroma	19	17
Transitional cell tumour	3	1
Tubular cell tumour	1	–
Renal Cyst	20	19
Pseudotumour	2	2
Diagnosis pending or symptoms unexplained	13	–
Renal abscess	1	1
A-V fistula	1	–
Bladder tumours	7	–

Table II

Isotope Calculations of Renal Mean Transit Times in Patients with Unexplained Loin Pain

	Vascular transit time	
Loin pain	Right	Left
R	13·2	1·6
L	6·6	*11·1*
L	*13·6*	*25·4*
R	*12·8*	6·4
R	9·1	5·2
R	*16·0*	12·9
R	8·2	6·0
L	8·7	9·2
L	6·9	*16·4*
Normal control values	9·0±2·8	8·3±2·0

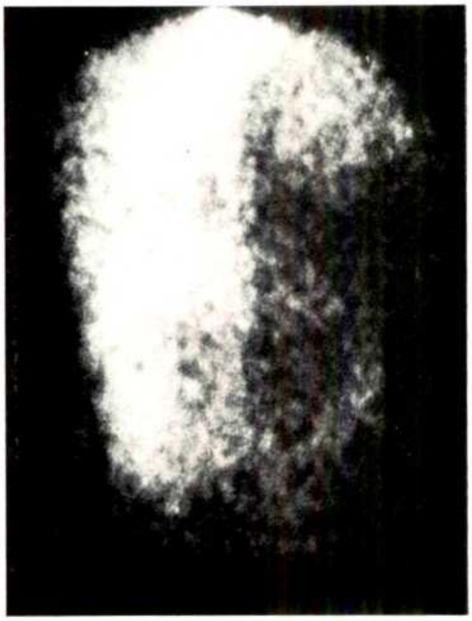

Fig. 5. Vascular study in patient with right hydronephrosis and traumatic right renal artery thrombosis, demonstrating extremely poor vascularisation.

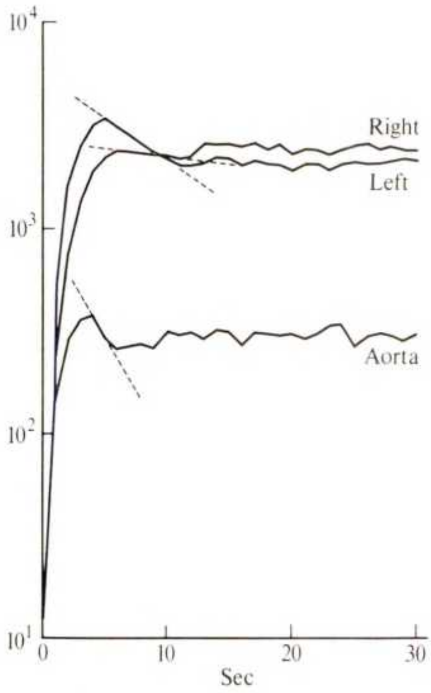

Fig. 6. Circulation curves derived from vascular study of patient with right renal vein thrombosis demonstrating the exponential fit for the calculation of mean transit time.

Summary

The technique of isotope renal scintigraphy using Technetium-^{99m} labelled agents and a gamma camera system on-line to a digital computer is described.

Its value in diagnosing renal space-occupying disease and renovascular abnormalities is emphasised. A method of measuring individual renal haemodynamics and the possible potential of such techniques are discussed.

Radio-isotope studies are rapid, simple, non-invasive and non-toxic. They give information complementary to that from urography.

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Our thanks are due to Mr Robin Barnard of the University Hospital of South Manchester for his help and permission to examine the patients under his care.

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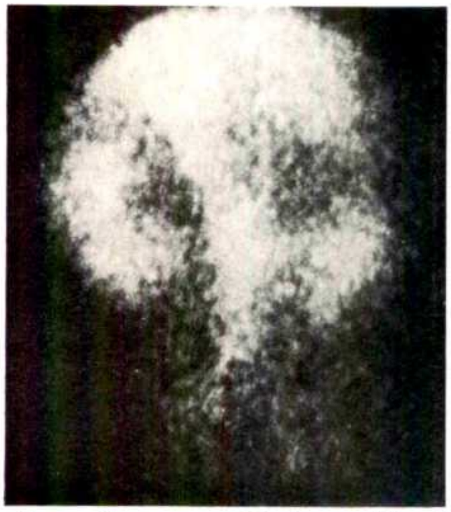

Fig. 7. Vascular study demonstrating large aortic aneurysm arising in area of the origin of renal arteries.

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The Authors

P. H. O'Reilly, FRCS, Research Fellow, Department of Urology.
R. S. Lawson, PhD, Physicist, Department of Nuclear Medicine and Medical Physics.
R. A. Shields, MSc, Principal Physicist, Department of Medical Physics.
H. J. Testa, MD, PhD, Consultant and Director, Department of Nuclear Medicine.
E. Charlton Edwards, MCh, MD, FRCS, Senior Consultant, Department of Urology.
R. N. P. Carroll, MD, FRCS, Consultant Urologist, Department of Urology.

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Computed Tomography of the Kidney

J. STRUYVEN, J. P. BRION, N. FREDERIC and C. C. SCHULMAN

Computed Tomography Unit and Department of Urology, University of Brussels, Belgium

Computed tomography (CT) is the reconstruction by computer of a tomographic section of the body using multiple X-ray absorption measurements.

The first attempt at medical application of image reconstruction was carried out by Oldendorf in 1961, Kuhl and Edwards in 1963 and Cormack in 1963. The development of the first clinical unit (head unit) was accomplished by Hounsfield (1973). The first total body scanner was developed by Ledley *et al.*, (1974).

Principle of CT

A CT scan equipment consists of a patient-handling table, an operator, a viewing console, a computer, the X-ray generator and a scanning gantry.

The X-ray scanner consists basically of a collimated X-ray tube rigidly mounted opposite a detector array (NaI, CaFe BGO Xenon. The X-ray beam, finely collimated, passes through the body and is recorded by the X-ray, detectors.

The gantry (X-ray tube—detector) makes two scanning motions: a translation and a rotation. At the end of the translation the gantry rotates over 1° to 20° and translates again. The entire motion covers 180° and makes about 3.10^6 measurements. The computer is used to process the data in an appropriate algorithm (computer program) to generate an image representing the pattern of attenuation coefficients in the cross-section of the patient. The computation procedure is reduced by imposing a coarse grid on the slice. Common grids used are a 256 × 256 to 320 × 320 matrix. These 65.356 points (256 × 256) are calculated in the slide or layer examined. The thickness of a slice (collimated beam) is 8-13 mm.

The computer displays the matrix on a video monitor using varying shades of greys or colours to represent the computed attenuation coefficients (CT numbers). This image reflects anatomical structures. A special display is used to measure the CT numbers (density) of any region of interest in numerical data. The TV monitor is photographically recorded to provide a permanent record. All information is stored on magnetic tape.

Material and Methods

Investigations were performed using an Ohio Nuclear Delta Scan which obtains two simultaneous 13 mm thickness slides in 2 min 30 sec. The scanner has an image matrix of 256 × 256. A cursor circle, variable in size and location, can measure attenuation numbers of any region of interest.

Patients are scanned in dorsal decubitus position without attempt to limit respiratory motion. Motion artefacts are reduced by administration of an antiperistaltic drug, usually 3 mg Glucagon I.M. A first series of 8 sections is performed without contrast media. The scanning is repeated after intravenous injection of 50-100 ml of Urografin 60% in a bolus. Most patients were referred to CT scan because of IVP abnormalities or non-functioning kidney. Other patients were investigated for haematuria, clinically suspected neoplasm or unproven renal pathology (Table I).

The diagnostic criteria employed in the CT evaluation of the kidney are: (*a*) alteration of the normal contour, (*b*) visualisation of a renal mass, (*c*) disappearance of perinephric outline and (*d*) measurements of attenuation coefficient in a region of interest.

Results

The results of CT evaluation are compared with pathological examination of the specimen, operative findings, cyst punctures or clinical evidence (Table II).

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Normal Kidney

The kidneys are well defined by CT scan because of the presence of perinephric and sinus fat which provides a clear outline of renal parenchyma. The renal contour is smooth and well delimited from peritoneal structures. A break occurs at the hilus when the vascular pedicle is directed anteromedially towards the aorta and the inferior vena cava. The renal parenchyma is homogenous. After administration of contrast media the shape of the calyces and renal pelvis is sharply defined. Without contrast media, normal parenchyma has an attenuation coefficient of 50-70 Delta Units and rises to 100-120 Delta Units after contrast enhancement. Renal veins are usually seen but arteries are demonstrated in about 20% of the cases.

Renal Neoplasms

A renal neoplasm may alter the outline and usually enlarges the kidney. The neoplastic parenchyma is not homogenous and has an attenuation value approximately equal to the normal tissue but after contrast the tumour enhances far less than the surrounding normal parenchyma. If the normal attenuation equivalent rises from 60 to 100 Delta Units, neoplastic tissue reaches 70-80 Delta Units. Another useful sign is the loss of the fat surrounding the kidney which most likely represents infiltration by the neoplasm. This sign is reliable in normal patients but less significant in very thin patients. An involvement of the hilus will be easily recognised.

29 cases out of 32 were operatively proven and confirmed by histology. 2 patients showed evidence of renal neoplasm (arteriography—cavography) but were considered inoperable. 1 case did not show any evidence of a renal tumour but a protruding mass was visible in the hilus. Arteriography showed an intrarenal neoplasm with extension in the renal hilus. Ultrasound diagnosis was that of a neoplasm and this was confirmed at operation. This case is considered as a false negative result.

Cysts

Renal cysts have sharp margins and are rounded structures on CT scan. Their attenuation value is 15 to ± 15 Delta Units and does not increase after injection of contrast medium. In this series most patients were referred to CT because of IVP abnormalities. Renal cysts are a very common finding in patients evaluated by axial tomography. Cysts of 1 cm are easily seen, especially when projecting beyond the cortex. Most cysts were confirmed by transcutaneous puncture. Cystic lesions can be aspirated under CT control.

Table I

CT Patients referred for Renal Diseases (179 Patients)

	%
IVP morphologic abnormalities	76
Non-functioning kidney	5
Postoperative evaluation	4
"Screening"	7
Others	8
Total (179 patients)	100

Table II

CT Findings

	%
Normal	13
Renal neoplasm	24
Cysts	40
Adenoma	2
Inflammatory lesions	3
Hydronephrosis	8
Renal aplasia	3
Retroperitoneal disease	4
Other	6
Total	103

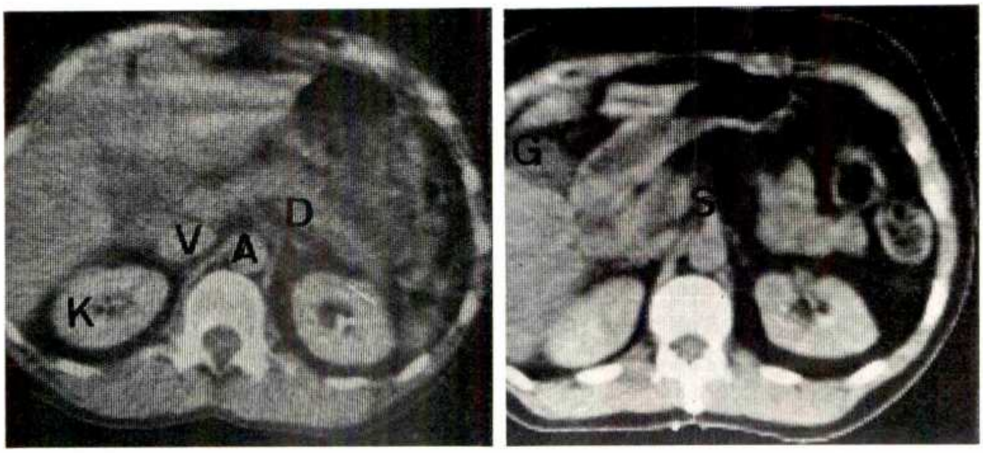

Fig. 1. Normal appearance of the kidneys: (K) well outlined by fat tissue; (A) aorta; (V) vena cava; (G) gallbladder; (P) pancreas; (S) superior mesenteric artery.

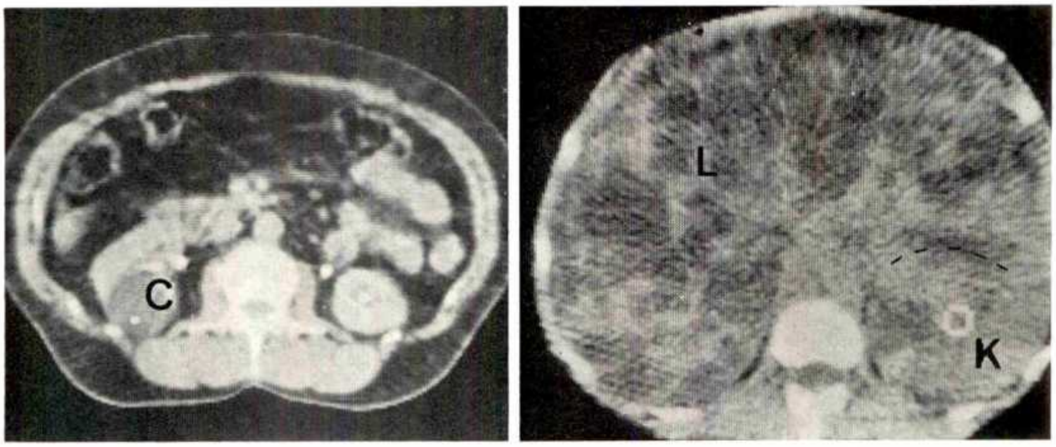

Fig. 2. *Left*—Typical cystic lesion with sharp parenchymal margin (C). Density: 5 Delta Units (Fluid). *Right*—Polycystic hepatic and renal disease in a thin female patient. The lack of perirenal fat explains the poor delineation of the left kidney.

Polycystic renal disease was correctly diagnosed by bilateral enlarged kidneys with lobulated contours, multiple cysts of variable size, distortion of calyces and parenchyma. The same examination allows the opportunity to detect cystic disease of the liver.

Adenoma

An adenoma showed as a lobulated parenchymal lesion with strong constrast enhancement which does not occur in neoplasm. Further experience has to establish if this is a pathognomonic sign.

Hydronephrosis

Urography cannot detect hydronephrotic non-functioning kidney even on delayed films after injection of high doses of contrast medium. Obstructive uropathy is easily recognised by axial tomography. The kidney is enlarged and attenuation value measurement shows low densities. If there is still any excretion, levels of contrast media can be seen in dilated calyces. CT is often able to recognise the origin of obstruction, for example by neoplastic involvement or calculus.

Inflammatory Lesions

Intrarenal abscesses are demonstrated by CT as lower density lesions (20 to 35 Delta Units) with less sharp delimitation than renal cysts. There is no contrast enhancement of the pathological area. Two cases were correctly diagnosed, the third was xanthogranulomatous pyelonephritis which appeared as a cyst on ultrasound but was defined as an inflammatory mass by CT.

Other Pathological Processes

CT aids in the diagnosis of renal atrophy or aplasia. Focal infarction is characterised by a marginal area which does not show contrast enhancement and the kidney seems normal prior to contrast injection. Only 1 case was investigated by CT and proven by arteriography.

Changes from the normal anatomy of the retroperitoneum can easily be recognised. Tumour masses are well profiled by surrounding fat. Muscles, aorta and inferior vena cava are well-

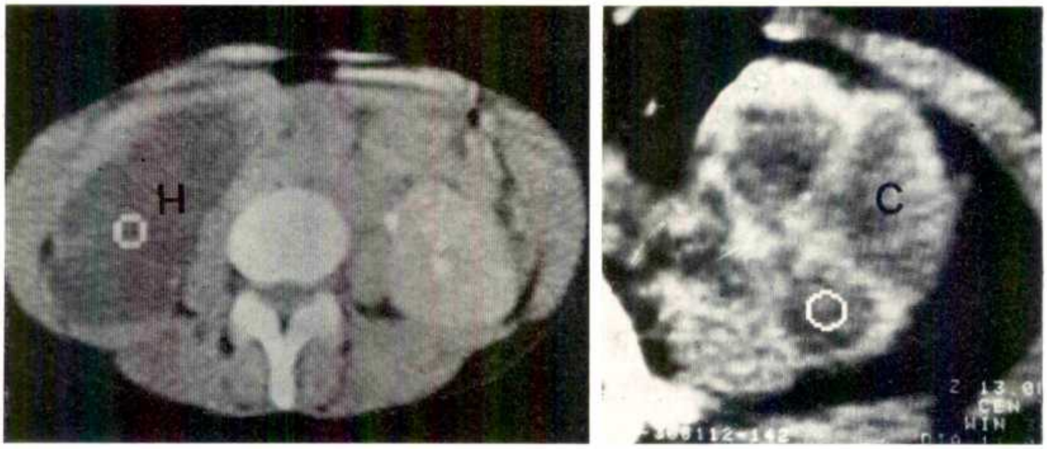

Fig. 3. *Left*—Hydronephrosis (H) of the right kidney caused by distal ureteric obstruction. Density: 1 Delta Unit. *Right*—Left kidney enlargement with dilated calyces (C). Density measurement: 34 Delta Units representing density between fluid and solid. Operative finding was pyonephrosis.

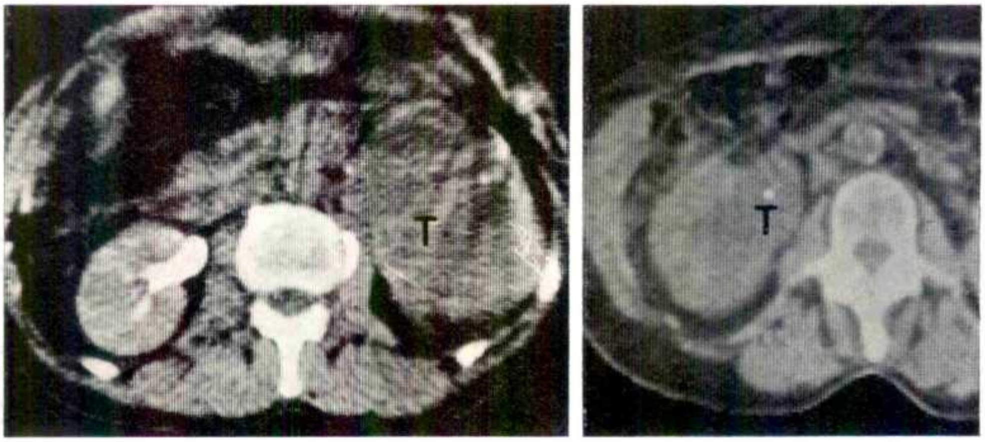

Fig. 4. *Left*—Typical aspect of renal neoplasm. The left kidney is heterogeneously enlarged and less enhanced by contrast medium then the normal kidney. *Right*—Neoplasm located in the renal pelvis without extrarenal extension.

defined structures and any malignant process will obliterate the tissue plane and obscure normal clear delineation of the retroperitoneal structures.

Discussion

3 erroneous conclusions were made in this study of 179 cases (17%). In the first case a false negative appeared to be a renal neoplasm without extension and enlargement. In the second, a large extrarenal pelvis, non-opacified by IVP, was diagnosed as a cyst, and because of a slight increase of density after contrast injection was suspected of containing a tumour. Arteriography gave the correct diagnosis. The third case showed an artefactual tumour in front of the lower pole of the right kidney.

A doubtful conclusion was given in 5 cases (2·8%). 2 renal neoplasms were detected in patients referred for investigation of another organ (liver metastasis).

As arteriography and ultrasound have a high rate of accuracy in the diagnosis of renal masses discovered on IVP, CT scan is not expected to play an important part in renal disease. However, experience shows that CT can diagnose most morphological diseases of the kidney. It is a non-invasive technique and obviates the need for ateriography in a significant number of cases. CT scan provides a diagnosis and defines the extent of neoplastic processes; it is considered as an excellent screening procedure since it has a high level of accuracy. The cost of the procedure remains quite high but where it is available, it should become part of the urological armamentarium for the diagnosis in selected cases.

Summary

The application of computed tomography to the diagnosis of kidney disease and the features of renal neoplasms, cysts, hydronephrosis, inflammatory parenchymal lesions and other pathological processes are described.

The diagnostic accuracy of computed tomography is excellent when compared with ultrasound and selective renal arteriography.

This new non-invasive technique can obviate the need for arteriography in a significant number of morphological diseases of the kidney and is especially useful in defining the extent of malignant tumours.

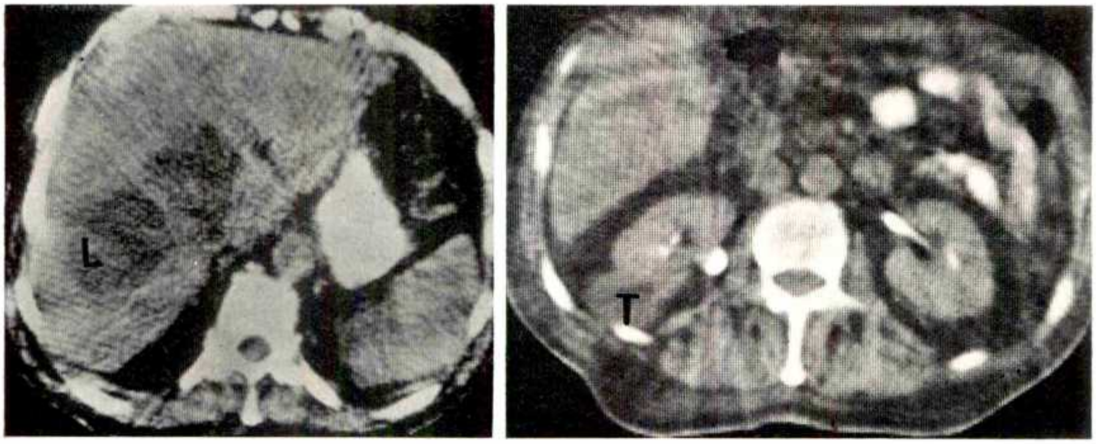

Fig. 5. Male patient, age 67, investigated by CT because of liver defects (L) found by scintigraphy and clinical suspicion of pancreatic disease. IVP was considered as normal. Neoplasm of the right kidney discovered by CT.

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The Authors

J. Struyven, MD, Radiologist.
J. P. Brion, MD, Radiologist.
N. Frederic, MD, Radiologist.
C. C. Schulman, MD, Urologist.

Requests for reprints to J. Struyven, Hôpital Brugmann—Department of Radiology, Place Van Gehuchten, 2, 1020 Brussels, Belgium.

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The Prevalence of Calcified Upper Urinary Tract Stone Disease in a Random Population—Cumbernauld Health Survey

R. SCOTT, R. FREELAND, W. MOWAT, MARY GARDINER, V. HAWTHORNE, R. M. MARSHALL and J. G. J. IVES

Royal Infirmary, Glasgow; Monklands and District General Hospital, Airdrie; University of Glasgow; and Glasgow Area Health Authority

The most common practice employed when referring to the "incidence" of stone disease is to relate the number of cases dealt with per 100,000 hospital admissions. Other methods of assessing "incidence" include surgical incidence, selected group incidence and true population sampling (Andersen, 1968).

No method is ideal and most are inaccurate in strictly epidemiological terms in that, before one can refer to the "incidence" of a disease, the "prevalence" figure must be known. In epidemiological terms the prevalence of a disease is the number of subjects who have the condition at a given time and the incidence is found by discovering the number of subjects who develop the condition in the population at a suitable interval after the prevalence figure is determined.

The present study was undertaken to assess the value of multiphasic screening to detect abdominal pathology with special reference to the prevalence of upper urinary tract stone disease in the new town of Cumbernauld.

Methods

A random sample (7,000) of the population was obtained from a computer record by a separate organisation (Cumbernauld Development Corporation). The population tends to the younger age-groups (Figs 1 and 2) but proof of the randomisation being effective is seen when the ages of the first 1,000 subjects studied were compared with Scotland as a whole (Fig. 3). The individuals were sent a specially designed record form. They were invited to attend the local health centre and, after checking the questionnaire, further details were obtained regarding urinary symptomatology. The height and weight for each individual were obtained and a plain abdominal radiograph was taken. A sample of blood was withdrawn and, after separation, analysed for urea, creatinine, calcium, inorganic phosphate, protein, alkaline phosphatase and urate values. A mid-stream sample of urine was checked for blood, sugar, protein and bile (Ames Labstix). A dip slide of the urine sample was incubated and after 20-24 hours was read for significant infection. The slides were impregnated with a nitrofurantoin/liquorice complex "Ceduran" (Tillots Lab.).

All abdominal X-rays were reported separately by 2 different consultants. Where the reports disagreed a third consultant acted as referee in reaching the final diagnosis. All subjects with possible calcified stones in the kidneys or gall bladder were asked to attend for intravenous urography or for cholecystography as appropriate. Biochemical and bacteriological abnormalities were rechecked.

The survey took place between 22nd January 1976 and 25th February 1977. The compliance rate was just under 50%, *i.e.* 3,398 persons appeared at the survey centre (1,650 males, 1,748 females). Of these, 106 subjects had no abdominal X-ray mainly because the subjects were female and could

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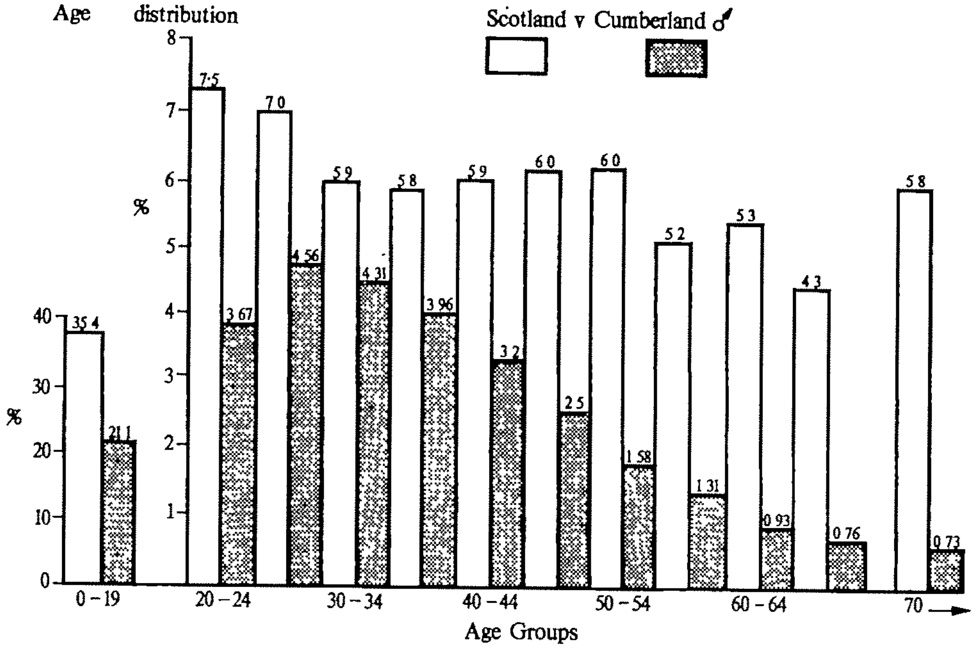

Fig. 1. Age distribution for men in Cumbernauld, Scotland.

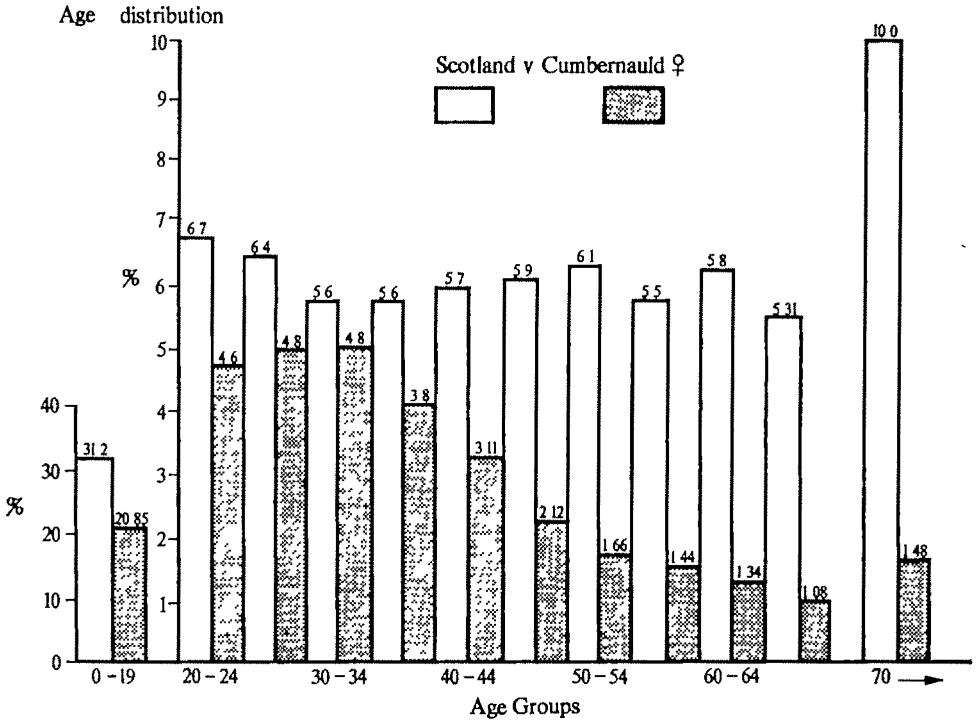

Fig. 2. Age distribution for women in Cumbernauld, Scotland.

not be X-rayed because (*a*) they were pregnant, (*b*) they were menopausal or (*c*) because of the "ten-day rule" and they did not attend when recalled. A few films were spoilt or the numbers were duplicated. In addition, 663 volunteers were interviewed (Table I). The first 2,000 subjects are now complete as at 31st May 1977 and the results of this sample are discussed.

Results—in 2,000 Subjects

(I) Radiological Abnormalities

As would be expected, the majority of radiological abnormalities were of a skeletal nature (Table II). The term osteoarthritis covers minor changes as well as gross findings. The study is designed to allow computer analyses of radiological abnormalities and symptomatology such as backache. One of the subjects with a secondary deposit was known to have a bowel carcinoma and was already undergoing X-ray therapy. The second was referred for investigation.

(II) Surgical or Potential Surgical Abnormalities (Non-urological)

Gall-stones were of immediate interest and to date 12 positive gall-stone cases have been identified (Table III). One man was diagnosed as having an aortic aneurysm and, on referral to a vascular surgeon, underwent surgery.

(III) Biochemical Abnormalities

Apart from the abnormal values obtained (Table IV), the biochemists now have a random population sample which can be classified in age and sex groups to give normal ranges. Of interest was

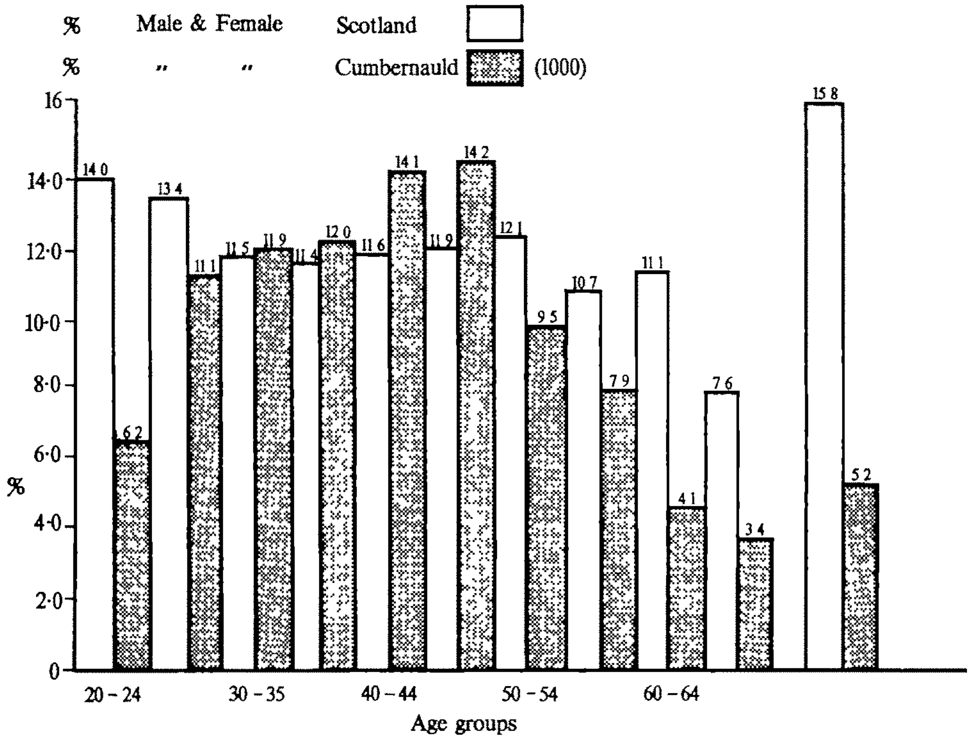

Fig. 3. Random sample ages in first 1,000.

the numbers with high urea and creatinine values—on rechecking most of these high values have not been substantiated. The blood urate values are also of interest as they have, on follow-up, revealed many persons with gout-like symptoms.

(IV) Bacteriological Abnormalities

As would be expected the rate of positive significant infection is higher in women (8·50%) than in men (1·25%) (Table V). This particular aspect of the study is dependent on good urine sampling. Those subjects with significant cultures have been followed up by checking mid-stream specimens of urine.

(V) Urinary Tract Abnormalities—Stone Prevalence

Those subjects who had possible calcified calculi in the kidneys have been followed up with intravenous urography (Table VI). Ureteric calculi are notoriously difficult to diagnose on a plain film and only those shadows which were agreed to be possible ureteric stones by all three consultants were investigated by urography. No ureteric stones have been proven so far but 2 subjects had ureteric calcification confirmed and one of these was due to tuberculosis.

In the first 2,000 subjects the prevalence of stone disease has been shown to be 3·83% with a male to female ratio of 1 : 1·05. The compliance rate for urography was good particularly among females (Table VII).

Table I

Epidemiological Survey—Cumbernauld 1976-77

Random sample	7,000
Attended survey	3,398
Volunteers	663
No X-ray undertaken	106
Total in random sample	3,292

Table II

Skeletal Abnormalities—2,000 Subjects

Type	Male	Female
O.A. Spine	602	527
Spina bifida occulta	197	153
Scoliosis	271	283
Osteoporosis	94	117
Transitional vertebra	35	66
Narrow disc space	23	37
Old T.B.	2	6
O.A. hips	16	6
Paget's disease	5	1
Minor abnormalities	48	125
Secondary deposit	1	1

Table III

Radiological Abnormalities (Possible) in Abdominal Viscera and Vasculature

Type	Male	Female
Possible gall-stones	23	30
Splenic calcification	4	10
Pancreatic calcification	1	1
Splenomegaly/hepatomegaly	5	17
Vascular calcification	125	78
Aortic calcification/enlargement	1	4
Minor findings	4	6
Gynaecological abnormalities	–	37

Table IV

Biochemical Abnormalities—2,000 Subjects

Type	Male	Female
High urea	88	59
High creatinine	126	35
High alkaline phosphatase	83	55
High urate (blood)	75	80
High calcium	25	31

Discussion

Proper population surveys of stone disease are rare (Ahlgren and Lorstad, 1965). With respect to Scotland we have found 2 conflicting statements regarding stone disease, viz. Thomas (1949) who states Scotland is an area of low incidence and Reaser (1935) who stated the opposite. Anderson (1964) in a survey of hospital admissions on the island of Lewis calculated the "incidence" to be 68 per 100,000 hospital admissions.

The concept of using hospital admission rates allows comparison to be made between hospitals but does not reflect the true prevalence of stone disease. There may be widely different local factors operating which are most obvious in large countries such as the USA, where an incidence figure of 94·7 per 100,000 does not bring out such subtle differences as exist between different states (Boyce, Garvey and Strawcutter, 1956).

Scandinavian authorities have tried to define geographical areas when referring to the incidence of stones by concentrating on one particular hospital in a relatively easily defined area (Hedenberg, 1951; Norlin *et al.*, 1976). Such figures, interesting as they are, may simply relate the referral rate or the radiodiagnostic facilities and many contemporary authors are clearly unhappy about hospital figures being true points of reference in determining "incidence" (Almby, Meirik and Schonebeck, 1975; Ljunghall and Hedstrand, 1975).

Previous work in our own unit suggested the prevalence of the disease to be of the order of 3 % (McKay *et al.*, 1975). The present work gives the prevalence rate in a random population and with

Table V

Urine Abnormalities—2,000 Subjects

Type	Male	Female
Dip slides—positive	25 (1·25 %)	163 (8·5 %)
Ceduran sensitive	22	152
Ceduran insensitive	3	11
Proteinuria	36	38
Glycosuria	52	13

Table VI

Abnormalities of the Urinary Tract—2,000 Subjects

Type	Male	Female
Possible stone right kidney	27	26
Possible stone left kidney	29	33
Possible bilateral stones	5	8
Possible ureteric stone	4	2
Prostatic calcification	12	–
Unequal kidney size	15	16
Possible bladder stone	1	
Possible prostatic carcinoma	5	–
Bladder implant	–	1

Table VII

Prevalence of Stone Disease—2,000 Subjects

	No. 0-1,000		No. 1,001-2,000	
Lesion	Male	Female	Male	Female
Stones—right kidney	6	6	5	11
Stones—left kidney	11	18	11	9
Bilateral calculi	–	–	2	–
Parathyroid adenoma	1	–	–	–
T.B. kidney	–	1	1	–
Calcified cyst	–	–	1	–
No I.V.P.	1	2	4	–
% Stones (proven)	4·1		3·5	
% Stones (2,000)	3·83			

such a figure it is possible to study particular groups within the population. It has helped to define such significant factors as a trace element poisoning in a specialised group of workers (Scott *et al.*, 1976).

Similarly, when other specialised groups are defined (Larsen and Phillips, 1962; Blacklock, 1965; Scott, 1971) then it is possible to speculate as to why any one of them do or do not have a significantly greater liability to suffer from stone disease.

The present survey has, by its multiphasic composition, helped to define a large number of variables which could be significant not only with respect to stone disease but such imprecisely studied data as the blood urate levels thought to be associated with coronary heart disease (Annotation, *Lancet*, 1969).

The use of the dip-slide technique has been further explored and has revealed a higher than expected number of positive results (Asscher, 1974). There is a good correlation between dip-slide accuracy and plate cultures (McAllister, 1973). It is recommended that technical staff should be employed to interpret these slides (McAllister, 1974) as a variable interpretation of the slides has been uncovered in this study. The technique, however, is clearly useful and especially valuable in symptomatic urinary tract infection.

Conclusion

The survey has proved useful. The prevalence rate (3·83%) of stone disease has been established in 2,000 subjects. Inter-group comparisons can now be made against the normal population in this area. Factors which are associated with stone disease or which may have a bearing on its progress have been studied and the true incidence of the disease is now obtainable in the future.

Summary

It is difficult to obtain the true prevalence of stone disease in a community.

A proper random sample of a population has been studied and a figure of 3·83% of calcified stones have been found in 2,000 subjects.

The significance of biochemical, bacteriological, skeletal and other surgical abnormalities is discussed.

It is now possible to study individual groups within the population with respect to stone disease.

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The Authors

R. Scott, FRCSG, FRCSE, Consultant Urologist, Royal Infirmary, Glasgow.
R. Freeland, DPH, DMRDRCP&S, Consultant Radiologist, Monklands and District General Hospital, Airdrie.
W. Mowat, DMRD, Consultant Radiologist, Monklands and District General Hospital, Airdrie.
Mary Gardiner, BSc, FRIC, Principal Biochemist, Royal Infirmary, Glasgow.
V. Hawthorne, M.D. MRCPG, Senior Lecturer in Epidemiology and Preventive Medicine, University of Glasgow.
R. M. Marshall, PhD, Senior Systems Designer, Glasgow Area Health Authority.
J. C. J. Ives, FRCSG, FCPath, Consultant Bacteriologist, Royal Infirmary, Glasgow.

Doctors Taking Part

Allam, B.
Bell, G.
Brown, D.
Cameron, A.
Campbell, Alexander
Campbell, Alistair
Campbell, Hazel
Donnelly, T.
Dumbuya, S.
Fitzpatrick, R.
Flint, E.
Gillani, Sema
Herd, G.
Iqhbal, M.
Johnstone, A.
Kirkpatrick, R.
Lawson, W.
Lonie, J.
Mearns, G.
Milligan, J.
Mills, E.
Orr, S.
Paterson, P.
Reavey, J.
Sorooshian, K.
Thomson, G.
Watson, M.
Yates, A.

Requests for reprints to Mr R. Scott, Consultant Urologist, Royal Infirmary, Glasgow.

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Diurnal Variation in Urinary Oxalate

T. B. HARGREAVE, A. SALI, C. MACKAY and MARGARET SULLIVAN
Departments of Urology and Surgery, Western Infirmary, Glasgow

Oxalate is a common constituent of urinary calculi and in a recent series was present in two-thirds of stones analysed (Sutor, Wooley and Illingworth, 1974). The urinary oxalate concentration necessary to cause calcium oxalate precipitation is more critical than that of calcium (Nordin *et al.*, 1969). Seasonal and diurnal variations in urinary calcium have been studied extensively, but there have been few reports on similar studies with urinary oxalate (Hodgkinson, Marshall and Cochran, 1971; Hallson, Kasidas and Rose, 1977). The advent of an enzymatic method of oxalate estimation has made it possible to detect small variations in urinary oxalate excretion (Hallson and Rose, 1974). The purpose of this study was to determine whether there was any variation in oxalate excretion during sleep and following meals.

Patients and Method

10 men with an indwelling catheter, because of acute retention of urine, agreed to participate. Only fit ambulant men with no previous history of calculi, gastrointestinal disease or other serious illness were included. Routine preoperative investigations excluded renal calculi, renal failure and metabolic disease. During this study, patients were on a normal diet without fluid restriction and had no special medication. The urine was collected hourly in separate containers and refrigerated until analysis. Collections were made without disturbance of sleep. In each container 0·5 ml of concentrated hydrochloric acid was used as a preservative. Oxalate was determined by the enzymatic method of Hallson and Rose (1974). The urine was well mixed but not filtered before analysis.

Results

Urine Volume

The hourly urine volume was low between 4 and 11 a.m. and high between midday and 9 p.m. as shown in Fig. 1. The mean 24-hour total urine output was 1,805 ml ± 371.

Urine Creatinine Concentration

The hourly mean creatinine concentrations are shown in the Table. The creatinine was maximal between 4 and 11 a.m. and minimal at 3 p.m.

Urine Oxalate Concentration

The hourly oxalate concentration is shown in relation to urine volume (Fig. 1) and calcium concentration (Fig. 2). The mean hourly oxalate concentration was 2·75 mg/100 ml ± 1·58 (0·306 mmol/l ± 0·176). The oxalate concentration was lower than the mean between midnight and 8 a.m. and higher than the mean at 11 a.m. and between 6 and 11 p.m.

Urine Calcium Concentration

The hourly calcium concentration is shown in relation to the oxalate concentration in Fig. 2. The mean hourly calcium concentration was 9·76 mg/100 ml ± 7·48 (2·44 mmol/l ± 1·87). Both calcium and oxalate concentrations were above the mean together at 11 a.m. and 11 p.m.

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Total Oxalate Output

The total oxalate output also varied throughout the 24 hours and was maximal during the day and evening and minimal from 3 to 10 a.m. (Fig. 3). The mean hourly total oxalate output was 1·67 mg ± 1·31 (0·019 mmol ± 0·015). The 24-hour total oxalate output was 38·4 mg ± 5·6 (0·427 mmol ± 0·062).

Discussion

Urinary oxalate concentration and output varied throughout the 24-hour period with increases during the waking hours and decreases during sleep. The concentration and output increased following breakfast, and then again following lunch there was a persisting increase until midnight. At 6 a.m. the creatinine concentration was high, urine volume low and oxalate concentration below the mean. At 11 a.m. the creatinine concentration was high, urine volume low and oxalate concentration higher than the mean. At 10 p.m. the creatinine concentration was moderate, urine volume moderate and oxalate concentration at the peak level for the 24 hours. It appears that oxalate concentration is not explained simply by variations in urinary volume or concentration.

The 24-hour oxalate output was 38·4 mg ± 5·6 (0·427 mmol ± 0·062) which is higher than the normal range reported by Hallson and Rose (1974) of 27·09 mg ± 7·11 (0·301 mmol ± 0·079). Our higher figures may be explained by the older average age of our subjects (66 years) or by the fact we did not filter urine before analysis in case this removed any oxalate crystals.

It was noticeable that the maximum urinary calcium concentration was at the same time as the maximum urinary oxalate concentration and it would appear the times most at risk for calcium oxalate precipitation in this group of men were 11 a.m. and 11 p.m.

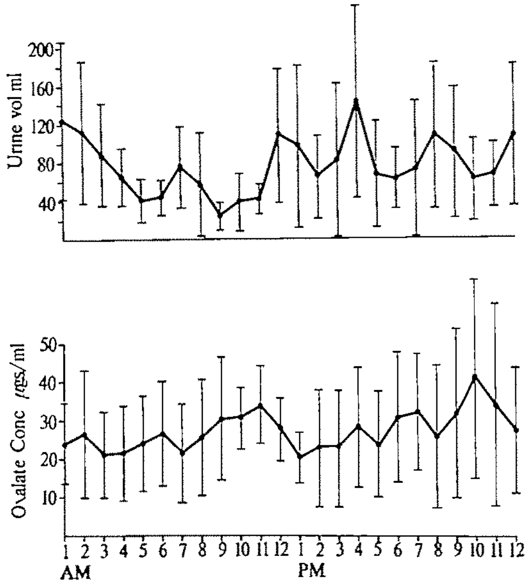
The persistent increase of urinary oxalate concentration and output which occurred in the evening could be explained by absorption of oxalate from solid food in both small and, possibly, large bowel, whereas the shorter morning increase is probably related to quicker absorption from oxalate rich fluids such as tea and coffee. It has been shown previously that ingestion of oxalate increases urinary oxalate (Barrett, 1942; Black, 1945; Zarembski and Hodgkinson, 1969). The earliest report (Zarembski and Hodgkinson, 1969) on daily variation of oxalate output in one normal subject showed increases in urinary oxalate excretion after meals and agrees with our findings. This subject was studied also during fasting and was found then to have little variation in urinary oxalate excretion. More recently these workers (Hodgkinson, Marshall and Cochran, 1971) have further studied a group of normal subjects and stone formers and note that the urinary oxalate rises to higher levels in stone formers but they do not clearly report the hourly variation

Table

Mean Hourly Creatinine Levels in 10 Normal Men

Time	mmol/l	mg/100 ml	Time	mmol/l	mg/100 ml
1 a.m.	8·35 ± 5·45	94·5 ± 61·7	1 p.m.	10·18 ± 10·09	115·2 ± 114·1
2 a.m.	8·88 ± 7·08	100·5 ± 80·1	2 p.m.	10·75 ± 7·04	121·6 ± 79·6
3 a.m.	8·37 ± 6·63	94·7 ± 75·0	3 p.m.	8·09 ± 4·59	91·5 ± 51·9
4 a.m.	11·03 ± 8·56	124·8 ± 96·8	4 p.m.	9·34 ± 7·05	105·7 ± 79·8
5 a.m.	15·22 ± 10·27	172·2 ± 116·2	5 p.m.	10·94 ± 7·27	123·8 ± 82·2
6 a.m.	17·00 ± 11·76	192·3 ± 133·0	6 p.m.	11·23 ± 7·20	127·0 ± 81·5
7 a.m.	11·06 ± 7·27	125·1 ± 82·2	7 p.m.	14·54 ± 10·81	164·5 ± 122·3
8 a.m.	12·69 ± 9·58	143·6 ± 108·4	8 p.m.	10·49 ± 6·94	118·7 ± 78·5
9 a.m.	22·00 ± 17·18	248·9 ± 194·4	9 p.m.	11·53 ± 9·20	130·4 ± 104·1
10 a.m.	19·27 ± 14·80	218·0 ± 167·4	10 p.m.	14·75 ± 7·85	166·9 ± 88·8
11 a.m.	18·63 ± 10·36	210·8 ± 117·2	11 p.m.	14·29 ± 7·17	161·7 ± 81·1
Midday	10·33 ± 3·94	116·9 ± 44·6	Midnight	11·11 ± 6·85	125·7 ± 77·5

in either group and no collections were made after midnight. In our study catheterised patients were chosen so as to enable urinary collection to be made throughout the 24 hours without disturbance of sleep. Marshall, Cochran and Hodgkinson (1972) found no difference between normal subjects and stone formers in their response to changes in dietary oxalate; however, they only studied the effect of a normal and low oxalate diet. Robertson, Peacock and Nordin (1971) found the addition of sodium oxalate to the basal diets of stone formers and controls resulted in a greater increase in oxalate in stone formers, and our own work in progress confirms this finding. It has been shown that patients with bile acid malabsorption (Dowling, Rose and Sutor, 1971; Smith, Fromm and Hofman, 1972) and steatorrhoea (Earnest and Graham, 1976) may develop hyperoxaluria. It is possible that some recurrent stone formers have similar gastrointestinal disorders which would result in increased urinary oxalate excretion following oxalate ingestion.



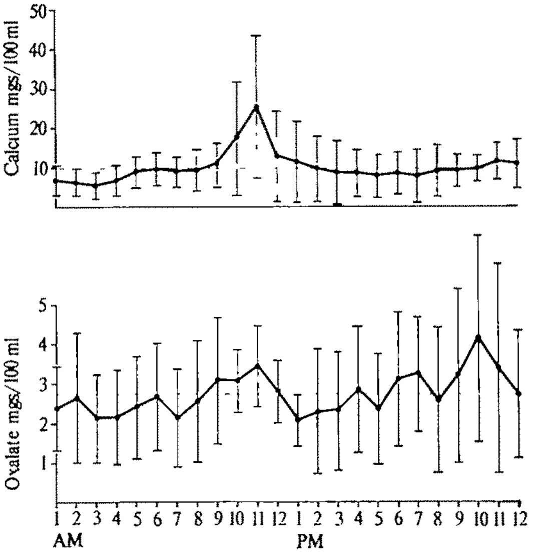


Fig. 1. 24-hour urine volume and oxalate concentration in 10 normal men. 1µg/ml oxalate ≡ 0 011mmol/l oxalate.

Fig. 2. 24-hour calcium and oxalate concentration in 10 normal men. 1 mg/100 ml calcium ≡ 0 25 mmol/l calcium. 1 mg/100 ml oxalate ≡ 0 11 mmol/l oxalate.

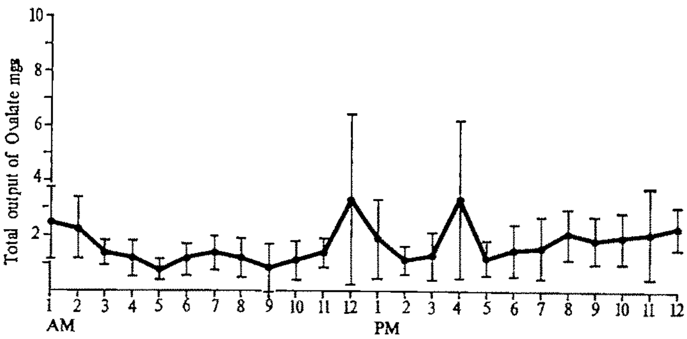


Fig. 3. 24-hour total oxalate output in 10 normal men. 1 mg oxalate ≡ 0 011 mmol oxalate.

Our results show that urinary oxalate concentration and output are greatest between 11 a.m. and 11 p.m. The most appropriate time to collect urine for oxalate estimation from stone formers to detect cases with a possible gastrointestinal disorder appears to be a 12-hour collection between these times.

Summary

The diurnal variation in urinary oxalate concentration and output was measured in 10 catheterised males.

There was an increase in urinary oxalate concentration and output during the day and evening and an early morning decrease.

It is thought that the daytime increase is related to dietary oxalate.

These data suggest an elevated urinary oxalate excretion is more likely to occur during the day and a 24-hour urine collection may mask this effect.

We would like to thank Mr A. G. Graham, Mr R. F. Deane and Mr K. F. Kyle, Department of Urology, for permission to study patients under their care.

We also thank Dr A. Fleck and Mr J. Sinclair of the Biochemistry Department for calcium and creatinine estimations.

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The Authors

T. B. Hargreave, FRCSE, Senior Registrar, Department of Urology, Western Infirmary, Glasgow.
A. Sali, FRCS, Department of Surgery, Repatriation Hospital, Melbourne.
C. Mackay, BSc, MB, ChB, FRCS, Senior Lecturer, Department of Surgery, Western Infirmary, Glasgow.
Margaret Sullivan, Laboratory Technician, Department of Surgery, Western Infirmary, Glasgow.

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Long-term Follow-up 100 Cases of Renal Calculi

M. W. SLEIGHT and J. E. A. WICKHAM
Department of Urology, St Bartholomew's Hospital, London

In 1974, 100 consecutive cases of pyelonephrolithotomy were reported using an ischaemic technique with regional hypothermia for functional protection (Wickham, Coe and Ward, 1974). The five-year follow-up of these cases is now reported with particular reference to:

1. Recurrent renal calculi.
2. Recurrence or persistence of urinary tract infection.
3. The effect on overall renal function.

Patients and Methods

Attempts were made to trace each of the patients in the original series. Where possible, they were reviewed by us, but when distance made this unreasonable, results were sent from their nearest hospital. Each patient traced was questioned and examined. Urine was sent for culture, a plain X-ray of the abdomen in inspiration and expiration and, on occasions, nephrotomography was performed. Blood was taken to estimate the serum creatinine.

79 patients were traced. Of these, 5 patients had died of unrelated causes and 2 had had the relevant kidney removed. This left 72 cases for study.

The mean follow-up for the whole group was 5·3 years with a minimum of 3·9 years (Fig. 1). Of the 72 cases, 58 had had stones composed of ammonium, calcium and magnesium phosphate which were associated with urinary infection; 14 stones were composed of pure calcium oxalate or cystine and were regarded as metabolic in origin, nearly always occurring in sterile urine (Table I).

Results

The Phosphate Stones

48 kidneys were completely cleared, as judged by X-rays during and after operation. Strict criteria were used to assess stone clearance and the presence of even minute fragments of radio-opaque material were regarded as a failed clearance operation. At follow-up, 41 remained clear and 7 had detectable stones; a recurrence rate of 14·5%. 10 cases, with phosphate calculi, had fragments left at operation. Of these 10, 6 showed a small but definite increase in size. 1 stone showed a significant increase and required re-operation. 3 remained unchanged (Fig. 2).

Infection Review

The infection rate in the 2 groups of stones differed greatly. On presentation, 78% of those with phosphate calculi were infected compared with only 14% of those with metabolic stones. This difference is statistically highly significant (Fig. 3). At follow-up, the infection rate of patients

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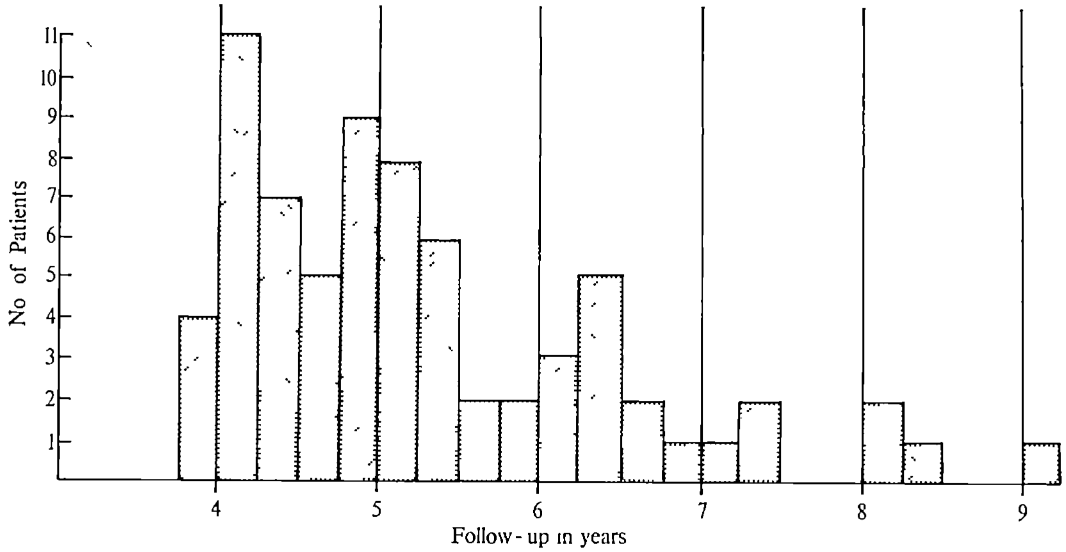


Fig. 1. Follow-up of nephrolithotomy using hypothermia.

with phosphate calculi depended upon the success of surgery. In the 48 cases in which the kidney was cleared, 10% were infected at follow-up. In the smaller group of kidneys with residual stones, 30% were infected (Fig. 4).

On further analysis of the 48 kidneys which were completely cleared, 43% of those who developed recurrent stone had a urinary infection whereas those who remained stone free showed only a 5% infection rate.

Considering the whole group of those with phosphate stones, those who are stone free have an infection rate of only 5%. Those who have stones, whether residual from the operation or due to recurrence, have an infection rate of 35% (Table II).

The Metabolic Stones

14 patients had metabolic stones. 11 were cleared at operation, but at follow-up, 3 had recurred. Of those who had residual stone, 2 were unchanged but 1 needed re-operation for a new stone.

At follow-up all patients with metabolic stones had sterile urine.

Table I

Stone Analysis in 72 Patients

	Male	Female	Total
Triple phosphate stone	11	47	58
Metabolic stone			
Calcium oxalate Cystine	9	5	14

Table II

Infection Status at Follow-up in 58 patients with Phosphate stones

	Total	No. infected	%
Stone free	41	2	5
Stones present (recurrent or residual)	17	6	35

$P<0{\cdot}01$; $\chi^2 = 6{\cdot}97$.

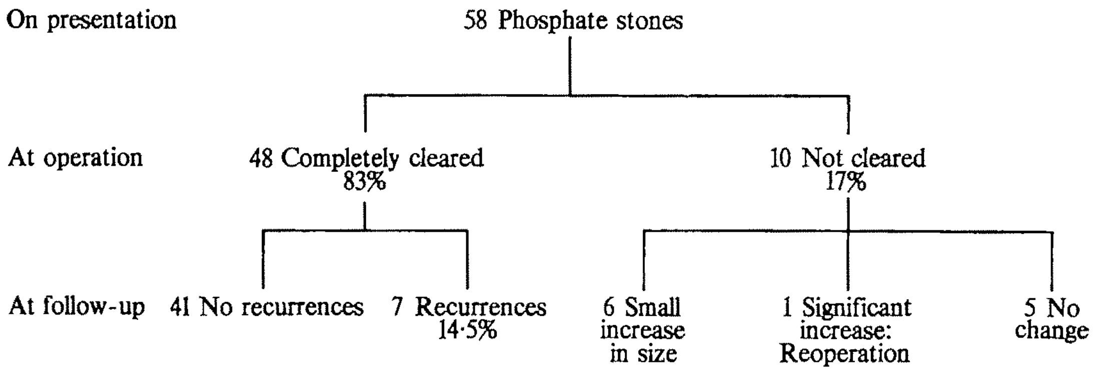
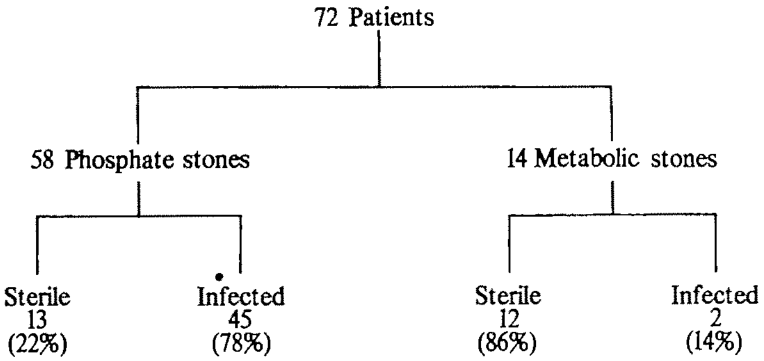


Fig. 2. Stone status in 58 patients with phosphate calculi.



$p < 0{\cdot}001 \; : \; \chi^2 = 17{\cdot}24$

Fig. 3. Infection status for all patients on presentation.

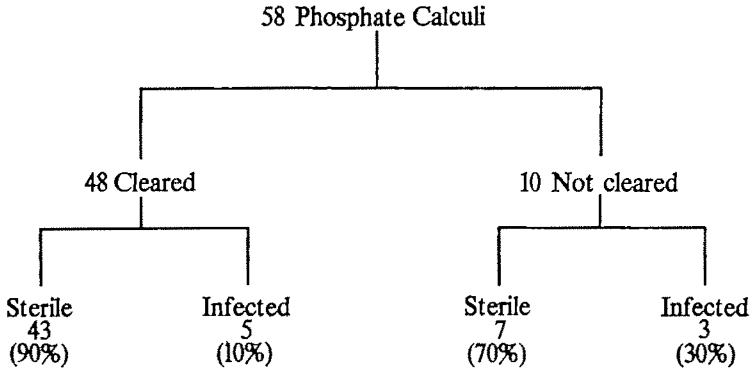


Fig. 4. Infection status at follow-up in 58 patients with phosphate stones.

Discussion

We consider that these figures again confirm that there is a fundamental difference between phosphatic and metabolic stones. The urine of patients with phosphate stones is usually infected, while that of metabolic stones is usually sterile. Complete clearance of stones leads to a sharp reduction in the rate of infection and those free of recurrent stone have the lowest rate of infection.

In the group of incompletely cleared kidneys infection is more frequent and the continued formation of stones can be serious. In patients with phosphate calculi complete stone removal should be the aim of surgery for what is a potentially curable disease.

In the metabolic group, stone removal is still followed by a considerable recurrence rate (Williams, 1972); this recurrence rate increasing with time. Despite painstaking stone removal, metabolically induced stone recurrence must be expected to be higher until adequate methods of controlling metabolic stone disease are available.

The role of infection is closely associated with phosphatic stones and the consistent presence of bacteria within this type of calculus has been clearly demonstrated by Delatte and Santos (1977) in electron-microscopic studies.

Renal Function

The mean serum creatinine level in 70 patients at follow-up was 125·1 μmol/l (range 50-478); the mean preoperative value for these patients was 125·6 μmol/l (range 53-283).

We believe that in these cases infection is the primary event as shown in 1 patient who presented with a staghorn calculus in a solitary kidney. Clearance was complete and the urine rendered sterile for 2 years. Re-infection with proteus, however, occurred perhaps because of poor drainage from rather baggy calyces shown on the excretion urogram, and a full staghorn calculus rapidly recurred. Re-operation again with complete clearance rendered the urine sterile. It is vital that follow-up of patients who have had phosphatic calculi should be long term and should include careful and frequent testing of the urine to control persistent infection and to detect re-infection.

It may well be that some of these patients need to be on long-term antibiotic therapy to avoid stone recurrence.

To obtain full and accurate stone clearance renal ischaemia is often necessary. Renal hypothermia was used to protect the kidney and these figures show that overall renal function seems to be unaffected.

Summary

Phosphatic calculi form in infected urine. Complete clearance is associated with sterile urine.

This disease is distinct from metabolic stone disease and should be curable if all stones are removed and postoperative infection is prevented.

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The Authors

M. W. Sleight, MChir, FRCS, Clinical Assistant to Department of Urology.
J. E. A. Wickham, MS, FRCS, Senior Consultant Urologist.
Requests for reprints to Mr J. E. A. Wickham, St Bartholomew's Hospital, West Smithfield, London, E.C.1.

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Partial Nephrectomy for Stone Disease

M. B. ROSE and O. J. FOLLOWS

Leeds and Bradford Hospitals and Bradford Royal Infirmary

Renal calculi frequently recur after they have been passed or removed, even though no cause for their formation can be found. The rate of recurrence increases the longer patients are observed (Williams, 1963; Blacklock, 1968). The risk of recurrence is not decreased by simple removal of the stone (Williams, 1972). However, it has been claimed that partial nephrectomy does reduce this risk (Stewart, 1960; Papathanassiadis and Swinney, 1966; Hans and Backer, 1972). Recently the operation has been condemned as unsuitable for the majority of renal stones because it involves loss of renal tissue without proven benefit (Anderson, 1974; Marshall *et al.*, 1975). However, there have been very few studies with the necessary prolonged and detailed follow-up after surgery to compare the results of partial nephrectomy with other operations. At Bradford partial nephrectomy was for many years commonly performed for renal calculi. The long-term results of this experience are now reported.

Patients and Methods

The hospital records of 253 patients who had a partial nephrectomy performed for stone between 1945 and 1973 were obtained from the records of the 2 urological surgeons at the Bradford Royal Infirmary. The patients were asked to attend the hospital. 63 came, 146 failed to come but their hospital records were adequate; 44 patients had inadequate records and were excluded.

From the notes of the 209 available patients, details were obtained about preoperative stone incidents and X-rays, operative details and X-rays, and postoperative complications. A stone incident was defined as the spontaneous passage of a stone, its removal or radiological evidence of a stone (Williams, 1963). Ureteric colic alone was not accepted as proof of a stone. Nearly all patients had X-rays taken soon after operation, and any stones shown on the first postoperative films (provided they were taken within a year of surgery) were considered to be residual calculi.

The aetiology of all stones was determined from the patient's history, stone analysis, urine culture, urography and biochemical investigations as recorded in the notes. If no cause for stone formation (apart from hypercalciuria) was found, it was assumed to be idiopathic.

The patients who attended hospital were asked about postoperative stone incidents. Plain X-rays of the renal tract were taken, and if suspicious opacities were seen, further films were taken. These were studied (by O. J. F.) without knowledge of the patient's history, and a decision made as to whether stones were present.

From the records of patients who did not attend, postoperative stone incidents were diagnosed from the history and X-ray reports. In doubtful cases the films were again reviewed independently.

True ipsilateral stone recurrences were defined as those occurring in the operated kidney when postoperative films had shown no residual stones. Stones first seen more than 1 year postoperatively and in the absence of previous films were assumed to be recurrences. True contralateral recurrences were those forming in the unoperated kidney if it was free of stones at the time of partial nephrectomy. Kidneys with residual stones and with contralateral stones present at operation were thus excluded from the calculation of the true recurrence rates, which were defined

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Table I

Partial Nephrectomies for Stone: Bradford 1945-73

	Number of patients	Number of partial nephrectomies			
		1	2	3	Total
Male	135	124	10	1	147
Female	74	69	4	1	80
Total	209	193	14	2	227

Table II

227 Partial Nephrectomies: Indications

	Small stones		Large stones	Anatomical abnormality and previous stones	Unknown	Total
	Single	Multiple				
Male	57	61	19	8	2	147
Female	37	25	15	3	0	80
Total	94	86	34	11	2	227

Table III

227 Partial Nephrectomies: Stone Aetiology

	Metabolic	Anatomical	Infective	Idiopathic	Total
Male	2	8	10	127	147
Female	7	4	18	51	80
Total	9	12	28	178	227

Table IV

227 Partial Nephrectomies: Part of Kidney Removed

Side		Pole removed			
Right	Left	Upper	Middle	Lower	Combination
106	121	36	6	179	6

Table V

227 Partial Nephrectomies: Length of Follow-up

Length of follow-up (years)	1-5	6-10	11-15	16-20	21-25	Over 26	Unknown
Number of patients	44	58	51	46	19	7	2

as the number of kidneys with true recurrences expressed as a percentage of kidneys under surveillance and at risk of recurrences at any given time after operation. In this way an accurate recurrence rate was determined for each year of follow-up.

Results

The partial nephrectomies are analysed in Table I; 12 patients had bilateral operations and 4 kidneys were operated on twice. The patients' ages at operation ranged from 2 to 76, with a mean of 44 years. Preoperatively 24% of patients had had more than 1 ipsilateral stone incident, and 37% 1 or more contralateral incident. The indications for operation are shown in Table II; large stones were those filling the renal pelvis or occupying more than 1 calyx. Anatomical abnormalities considered to be the site of stone formation were deformed calyces and localised renal calcification.

The number of true ipsilateral recurrent stones was not significantly different after operations for single or multiple stones, small or large stones, or for first or recurrent stones.

The aetiology of the stones is given in Table III. Metabolic causes were hyperparathyroidism (5) and cystinuria (4). Anatomical causes were hydronephrosis (4), duplex kidney (2), calyceal cyst (2), medullary sponge kidney (2) and prolonged recumbency (2). All 28 infective stones were associated with persistent urinary infection; the 15 that were analysed contained magnesium ammonium phosphate. Of the 178 presumed idiopathic stones all the 83 analysed contained calcium oxalate with or without phosphate. 137 patients with these stones had serum calcium estimations; all were normal. The urinary calcium excretion of 96 of these patients was measured,

Table VI

227 Partial Nephrectomies: Further Stone Formation

		Ipsilateral		Contralateral	
Stone aetiology	Operations	Residual stones	Recurrent stones	Stones present at operation	Recurrent stones
Metabolic	9	2	2	2	3
Anatomical	12	1	2	1	3
Infective	28	3	3	11	2
Idiopathic	178	10	36 (21%)	36	26 (18%)
Total	227	16	43 (20%)	50	34 (19%)

Percentage recurrences are of kidneys at risk.

Table VII

Operative X-rays and Further Stone Formation

	Kidneys	Residual stones	True recurrent stones	Mean time to recurrence (years)	Mean follow-up (years)
Calcification remaining	27	6	6	9·3	11·0
No calcification remaining	66	0	8	14·5	11·7

and hypercalciuria (24-hour excretion over 250 mg (6·25 mmol) for males, 200 mg (5 mmol) for females) found in 62.

The part of the kidney removed is shown in Table IV. Complications recorded included death in hospital (2 patients), nephrectomy (3 kidneys), secondary haemorrhage (once) and urinary fistula (3 times).

The mean follow-up time was 11·9 years from operation, with a range of 1 to 34 years. The distribution is shown in Table V.

The total number of residual and true recurrent stones after operation is given in Table VI. Of the 43 ipsilateral recurrent stones, 12 were removed by later operation and 7 passed spontaneously, the other 24 remained in the kidney. For the 34 contralateral recurrences the equivalent numbers were 5, 7 and 22.

The results of X-rays of the exposed kidney taken at operation were recorded on 93 occasions. When calcification was still seen at the end of the operation 44% of these kidneys formed more stones, but when none was seen only 12% did so (Table VII). This difference is statistically significant ($P < 0{\cdot}005$).

The true recurrence rates of ipsilateral and contralateral stones for each postoperative year are shown in Fig. 1 and Table VIII; the differences between the 2 rates are not statistically significant. In Fig. 2 the true ipsilateral recurrence rate for idiopathic stones alone is compared with the equivalent recurrence rate after other operations for calcium stones (Williams, 1972). At 15 and 20 years there is a statistically significant difference between the rate after partial nephrectomy and that after the other 3 operations ($P < 0{\cdot}01$ in all cases).

Discussion

This series of partial nephrectomies for stone appears to be largest reported in the English literature. Some of the patients are among those reported by Stewart (1960), who found a recurrence rate of 6·4% after 202 operations followed for an average of 6·3 years. Because of the interest in stone disease at Bradford (Carr, 1954) the radiological examinations have been thorough, the records detailed, and the follow-up prolonged. For this review, new information was obtained on 63 patients. Doubtful X-rays have been reviewed independently.

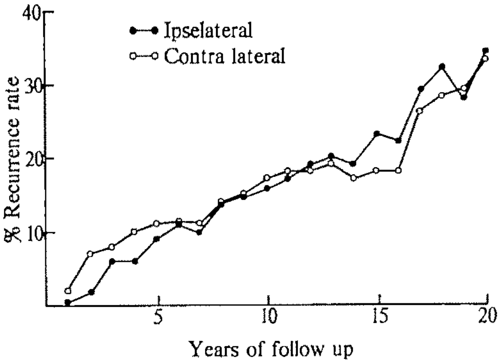
The definition of recurrent and residual stones used here has meant that, in doubt, a stone forming after operation is classified as a recurrence. The recurrence rate, being expressed as a percentage of the kidneys at risk and under surveillance, is a more accurate measure than the usually used crude percentage of all operations, and is the same as that employed by Williams (1972).

Although most patients were investigated, some stones may have been wrongly classified as

Table VIII

227 Partial Nephrectomies: True Recurrence Rates

	Ipsilateral			Contralateral		
Time from operation (years)	Kidneys at risk	Kidneys with recurrent stones	% Recurrence rate	Kidneys at risk	Kidneys with recurrent stones	% Recurrence rate
5	175	15	9	145	16	11
10	126	20	16	101	17	17
15	75	17	23	56	10	18
20	32	11	34	24	8	33



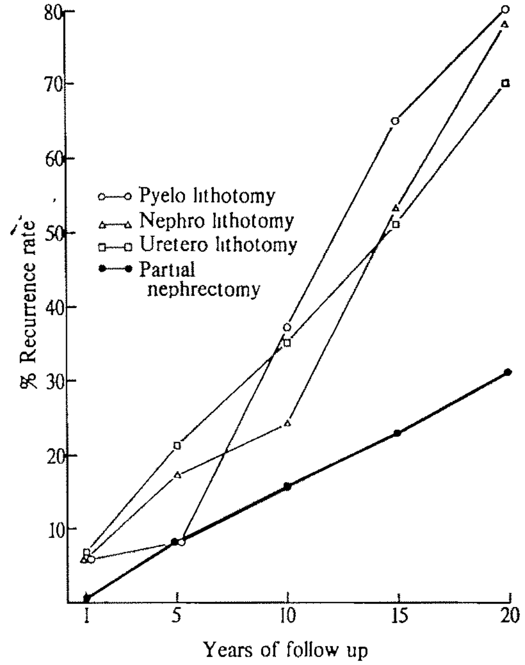


Fig. 1. 227 partial nephrectomies: true recurrence rates

Fig. 2. True ipsilateral recurrence rates after operations for idiopathic stones. Figures for pyelo-, nephro- and ureterolithotomy taken from Williams (1972).

idiopathic. For this reason all the operations were considered together. The recurrence rates of the idiopathic group is very similar to the total population (Table VI, Figs 1 and 2).

It has been shown that radiologically visible renal calcification remaining at the end of the operation makes further stone formation likely (Table VIII). Moreover, true recurrent stones appear sooner. This strongly suggests that renal calcification promotes stone formation (Randall, 1937; Carr, 1954). However, there is no evidence that partial nephrectomy encourages the passage of any recurrent stones, as was suggested by Papathanassiadis and Swinney (1966).

The recurrence rate after partial nephrectomy increases with time, as in most other studies of stone formation, and is the same in the operated as in the unoperated kidney. It is, moreover, half that found in a similar study of other stone operations done in Leeds (Williams, 1972). Other series have also suggested that partial nephrectomy is followed by fewer recurrent stones than less radical procedures (Williams, 1963; Papathanassiadis and Swinney, 1966), although only overall recurrence rates were calculated and the follow-up periods varied, making true comparison impossible.

As this series and that reported from Leeds are directly comparable, it appears that partial nephrectomy reduces the risk of recurrent stone formation. The average weight of renal tissue removed in a recent series of 35 partial nephrectomies for stone was approximately 30 grams (Anderson, 1977), *i.e.* one-fifth of the weight of a normal kidney. Even after increasing the demonstrated recurrence rate by 25% to allow for this loss of potentially stone-bearing tissue, the rate is considerably lower than that reported by Williams (1972), suggesting that kidney ablation is not the whole explanation for the difference. Other long-term studies have shown that after operative removal or the passage of a stone, recurrence is more common in the same kidney than the opposite one (Sutherland, 1954; Williams, 1963; Blacklock, 1968). This suggests that, although stone formation is primarily a biochemical event occurring in the urine (Robertson, Peacock and Nordin, 1971), anatomical factors may decide *where* a stone develops (Rose, 1976). It may be that stone formation causes a local abnormality of the kidney which persists and predisposes to more stones. Partial nephrectomy, if it removes this abnormality, should reduce stone recurrence to a minimum, which being determined by the urine would be the same for both kidneys. This is a possible explanation for the close similarity between the ipsilateral and contralateral recurrence rates after partial nephrectomy.

Whatever the reason for the reduced recurrence rate after partial nephrectomy, the finding suggests that the operation should be considered more often in the management of renal stone disease.

Summary

The results of 227 partial nephrectomies for stone were reviewed.

Radiologically visible calcification remaining in the kidney at the end of the operation increased the risk of further stone formation.

Ipsilateral and contralateral true recurrence rates after partial nephrectomy were the same, and increased with time up to 34% at 20 years.

Ipsilateral recurrence rates after partial nephrectomy were half those found in a similar study of nephrolithotomy, pyelolithotomy and ureterolithotomy.

Anatomical factors are important in stone formation, and partial nephrectomy is of value in the management of renal stones.

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The Authors

M. B. Rose, MA, MB, MChir, Senior Registrar in Urology, Leeds and Bradford Hospitals. (now Consultant Urologist, Morriston Hospital, Swansea).

O. J. Follows, FRCR, MRCP, Consultant Radiologist, Bradford Royal Infirmary.

Address for offprints: Mr M. B. Rose, Department of Urology, Morriston Hospital, Swansea, Glamorgan.

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Can Angiography stage Renal Carcinoma?

G. DAS, G. D. CHISHOLM and T. SHERWOOD

Urological Unit and Department of Radiodiagnosis, Hammersmith Hospital, and Royal Postgraduate Medical School, London

Arteriography maps out the abnormal tumour vessels in renal carcinoma, and it is tempting to use this information for judging tumour extent as well as for diagnosis (Kahn, Wise and Robbins, 1968; Lang, 1971). Because of the difficulties of assessing retroperitoneal swellings by palpation, clinical bedside methods will not serve this end reliably. The importance of preoperative staging by angiography is underlined by the recommendation of the International Union Against Cancer (U.I.C.C.) that renal carcinoma cannot be staged properly on the TNM system without an arteriogram. In the absence of an arteriogram a renal carcinoma receives a TX label: "the minimum requirements to assess fully the extent of the primary tumour cannot be met" (Wallace, Chisholm and Hendry, 1975). This view of arteriography as an essential and reliable preoperative staging exercise can be challenged (Brindle, 1972; Buist, 1974), and we report here on relating radiological to operative and histopathological findings in 36 patients with renal carcinoma.

Methods

All patients with renal carcinoma seen by the urology team at Hammersmith Hospital and by one of us (G. D. C.) at St Peter's Hospital have been reviewed. We included all patients who came to surgery and whose angiograms, operative and histopathological findings were available. Disposal of old X-rays limited this study to the past 10 years.

Arteriograms

We reviewed jointly all available angiograms. These usually included an abdominal aortogram followed by selective arteriography of the involved kidney. Standard AP projections with rapid serial filming were used with few exceptions and selective injections of lumbar or other non-renal arteries were not usually done. The tumour was staged without knowing operative or pathological findings:

"T0 No evidence of primary tumour.
T1 Evidence of a small tumour without enlargement of the kidney. There is limited calyceal distortion or deformity and circumscribed vascular deformities, surrounded by renal parenchyma.
T2 Evidence of a large tumour with deformity and/or enlargement of the kidney or calyceal or pelvic involvement. The continuity of the cortex is preserved.
T3 Evidence of spread into perinephric fat, peri-pelvic fat or hilar vessels.
T4 Evidence of invasion into neighbouring organs or abdominal wall". (Wallace, Chisholm and Hendry, 1975.)

Histopathological staging of P0-P4 could be given for all tumours on the basis of operation and pathology reports:

"P1 Tumour surrounded by renal parenchyma.
P2 Tumour extending to the capsule and/or invading the renal pelvis and/or calyces.

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P3 Tumour extending beyond the capsule into the perinephric fat or the peri-pelvic fat or the renal pedicle.

P4 Tumour invading neighbouring organs and/or fixed to the abdominal wall." (Wallace, Chisholm and Hendry, 1975.)

Results

The Table shows the main agreements and disagreements between angiogram (T) and final (P) staging.

Whilst the angiogram staged the tumour correctly in the majority of patients (21), there were sizable groups of overstaged (8) and understaged (6) patients. In 1 patient with a sarcomatoid renal carcinoma, presenting with obvious clinical and urographic signs of tumour, this diagnosis could not be made with confidence on the arteriogram. Excluding this patient, incorrect preoperative staging erred by one step on the T/P system (Fig. 1).

T3/P2 was the only preoperative overstaging error and the most common mistake overall, *i.e.* a tumour apparently invading through the renal capsule or hilum on arteriography (Figs 2a and b).

There was an additional patient outside the series with the preoperative diagnosis of T3 renal carcinoma. Histopathological findings after nephrectomy were in fact of an angiomyolipoma with a P2 stage as would be expected of this benign tumour. The mass received part of its blood supply from extrarenal vessels on arteriography, dramatically illustrating our difficulties in staging.

Discussion

This study suggests that the standard abdominal aortogram and selective renal arteriogram cannot always stage a renal carcinoma accurately. The error rate (14 patients in 35 tumour diagnoses = 40%) appears high. It is instructive to inquire why this should be so.

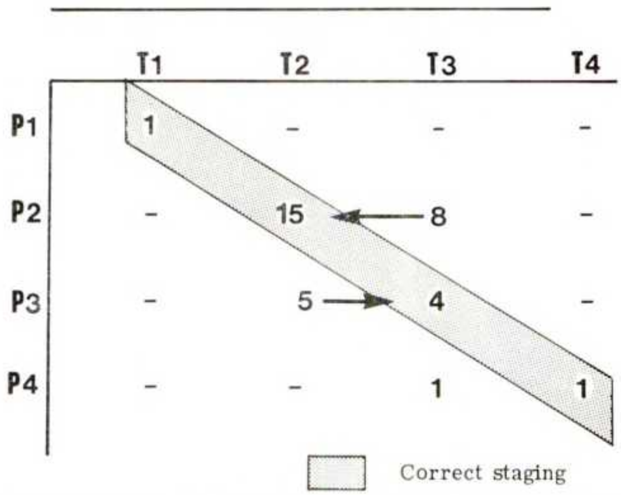
Preoperative overstaging, our commonest error, is particularly related to the extraordinary local deformity possible with renal tumours. There may be gross bulging of the kidney border with abnormal tumour vessels spreading well beyond the reniform contour, to suggest a growth invading the peri-renal tissues freely. Yet histopathological study may still show a thinned renal capsule stretched over this mass, effectively confining the tumour (P2). It might be thought that more sophisticated angiographic techniques should unravel this difficulty, for instance by selective injection of extrarenal arteries which may supply a P3 tumour. Brindle (1972) and Buist (1974), however, have shown in such studies that this expectation is not fulfilled. Even tumours with vessels fed by extrarenal arteries, like the lumbar, can still be wholly intrarenal (P2). Such angiograms provide evidence of an avid collateral supply to the mass, but not of tumour extension.

Table

Angiogram (T) and Final (P) Staging

	Patients
Agreement on T and P stage	21
False preoperative overstaging (T > P)	8
False preoperative understaging (T < P)	6
Tumour not diagnosed on angiogram	1
	36

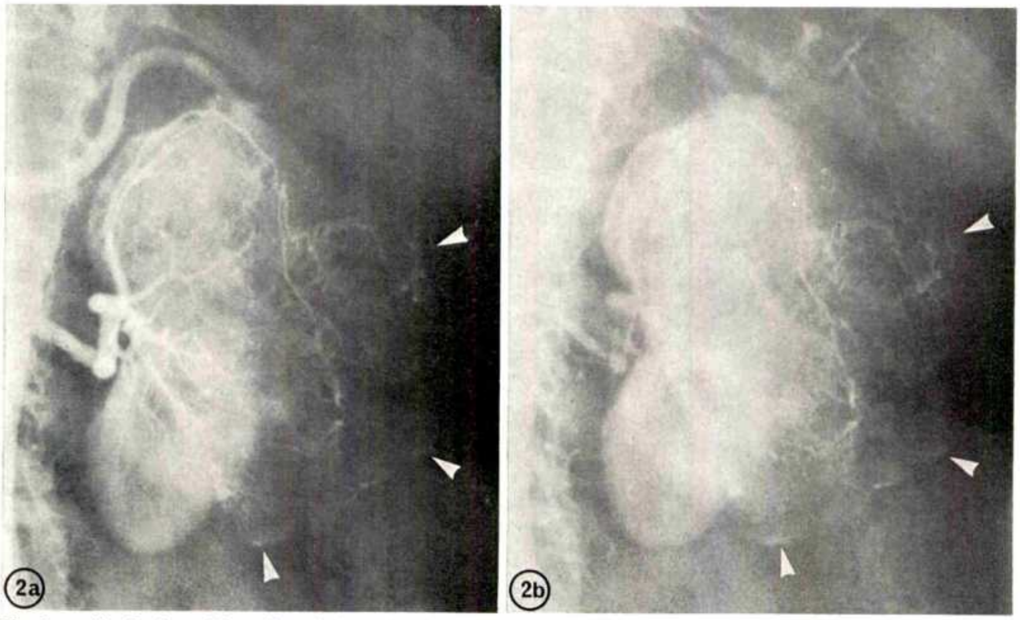
Preoperative overstaging errors are therefore determined by the behaviour of renal carcinomas. They are mirrored by overstaging at surgery, where the kidney may be found stuck down, as if by extrarenal spread: pathological studies may still show only benign adhesions with a wholly intrarenal growth. Preoperative understaging is more dependent on angiographic shortcomings. In standard AP projection any solely anterior or posterior transcapsular tumour spread will not be seen, and accounts for at least two of our errors here. An appreciable proportion of renal carcinoma is avascular (McLaughlin *et al.*, 1974) and judging the extent of such lesions without abnormal vessels as markers is difficult or impossible.



	T1	T2	T3	T4
P1	1	–	–	–
P2	–	15	8	–
P3	–	5	4	–
P4	–	–	1	1

▨ Correct staging

Fig. 1. Errors in staging by angiography (T) as determined by histopathology (P), excluding one T0/P2 patient (see text).



Figs 2a and b. Early and late films during selective renal angiography show an extensive carcinoma, with abnormal vessels apparently transgressing the peri-renal fascia (arrows). This was, however, a P2 tumour with an intact renal capsule.

In view of these findings we question the accuracy of T staging of renal carcinoma by angiography, and the need for routine arteriography of all such tumour suspects. The investigation still has a useful place in confirming the diagnosis, now often made by ultrasound and in showing details of the operative problem for the surgeon, particularly the state of the renal vein. The demonstration of a normal contralateral kidney to allow total ipsilateral nephrectomy is also firmer on angiography than urography. However, in the standard approach to renal masses beginning with the intravenous urogram and the ultrasound scan (Sherwood, 1975), the diagnosis of renal carcinoma and the correct management by nephrectomy are often very clear indeed. This is particularly so when cytological studies show carcinoma cells in the urine (Highman and Sherwood, 1978). We do not think that routine arteriography can then be justified with correct staging as the only remaining indication. The arteriogram is here being asked a question it cannot answer with any accuracy. Staging by histopathology is the essential assessment needed for advising and managing patients with renal carcinoma.

Summary

We have compared the staging of renal carcinomas in 36 patients as judged preoperatively by angiography (T stage) and postoperatively by histopathology (P stage).

Using the standard abdominal aortogram and selective renal arteriogram we found a considerable error rate in T staging (40%). The commonest error was preoperative overstaging, and this is probably determined by the behaviour of renal carcinoma, rather than by inadequate angiography.

We conclude that whilst renal arteriography remains a useful diagnostic aid, it cannot answer questions on tumour extent with any accuracy.

Staging by histopathology is essential for proper assessment and management of these patients.

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The Authors

G. Das, MS, FRCS, Registrar (Urology).
G. D. Chisholm, ChM, FRCS, Senior Urological Surgeon and Senior Lecturer.
T. Sherwood, MRCP, FRCR, Senior Lecturer and Hon. Consultant Radiologist.

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The Obstructed Kidney: Correlation between Renal Function and Urodynamic Assessment

H. N. WHITFIELD, K. E. BRITTON, I. KELSEY FRY, W. F. HENDRY, C. C. NIMMON, P. TRAVERS and J. E. A. WICKHAM

Departments of Urology, Nuclear Medicine and Radiology, St Bartholomew's Hospital, London

The diagnosis of upper urinary tract obstruction may be difficult. Where hydronephrosis exists it is not always possible to differentiate radiographic appearances which are secondary to obstruction from those persisting after obstruction has been relieved or from changes due to ureteric reflux.

Antegrade pressure/flow studies enable the diagnosis of upper urinary tract obstruction to be defined urodynamically (Whitaker, 1973) but give no information about renal function.

Differential renal function may be measured isotopically but the diagnosis of obstruction by conventional renography is unreliable, since a prolonged excretion phase may be due either to obstruction or to a mixing effect secondary to isotope stasis in a capacious but unobstructed renal pelvis. It remains to be established whether gamma camera renography is a more accurate method of diagnosing obstruction than conventional probe renography.

We report the results of simultaneous radiographic, renographic and urodynamic studies in patients with pelvi-ureteric junction obstruction.

Patients and Methods

20 patients presenting with possible pelvi-ureteric junction obstruction were investigated.

16 of these patients underwent radiographic, renographic and urodynamic studies. In the remaining 4 patients antegrade pressure/flow studies were not completed due to failure to puncture the renal pelvis in 2 cases, an apparatus failure in 1, and in 1 patient with a radiographically completely obstructed kidney renal puncture was thought to be inadvisable.

High-dose intravenous urography (IVU) (0·6 mg iodine/kilo body weight) was performed in the hydrated patient. 40 mg frusemide was given intravenously 20 min after the injection of contrast and 5 features were examined:

(*a*) The size of the renal pelvis 20 min after injection of contrast and the size 15 min after frusemide injection were measured by a computer-assisted technique which has been previously described (Ward, Franklin and Wickham, 1976). A graphic tablet with a pressure sensitive surface was linked on-line to a computer and the renal pelvis was outlined and its area expressed in square centimetres. The percentage change in the size of the renal pelvis before and after frusemide was calculated.
(*b*) The calyceal size before and after injection of frusemide.
(*c*) The contrast dilution effect within the renal pelvis following frusemide.
(*d*) The presence of ureteric filling at any time during the investigation.
(*e*) The occurrence of pain during the investigation.

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Antegrade pressure/flow studies were performed by perfusing saline at the rate of 10 ml/min through a 19 gauge needle and recording intrarenal pelvic pressure through a side arm catheter via a transducer the output of which was displayed on a chart recorder. Obstruction was held to be present when a pressure rise occurred within the renal pelvis of more than 15 mm Hg. Perfusion was continued for 20 min after the renal pelvis was judged to have been filled or until a diagnostic pressure rise was achieved.

Renography was performed using ^{99m} Technetium DTPA, an agent filtered by the glomerules, in a dose of 10 mCi. Using a conventional background subtracted renographic technique 2 features were examined, the excretory phase of the renogram and differential renal function. Where a prolonged excretory phase was associated with diminished renal function a diagnosis of obstruction was made, but where a prolonged excretory phase occurred in the presence of normal differential renal function a diagnosis of a mixing phenomenon without obstruction was made.

A computer-linked system was employed to record the data in a series of 100 10-sec frames. From the gamma camera images, regions of interest around the kidney and renal pelvis were delineated. In addition data was simultaneously recorded on punched paper tape from a

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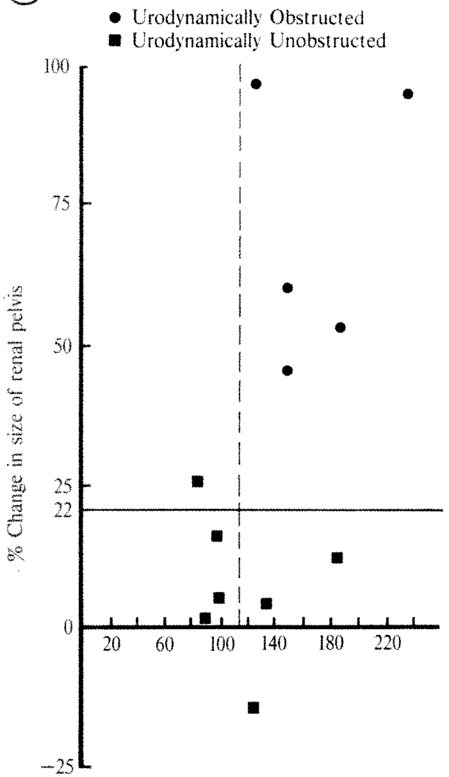

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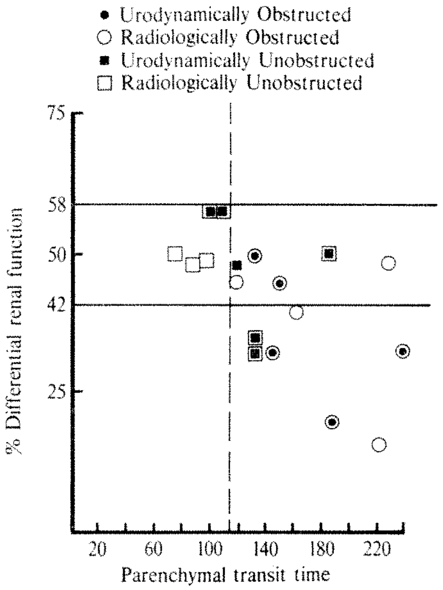

Fig. 1. Correlation between pressure/flow studies, percentage increase in renal pelvis size after frusemide and deconvolution analysis of the gamma camera renogram.

Fig. 2. Correlation between differential renal function, deconvolution analysis of the gamma camera renogram and radiological and urodynamic results.

scintillation probe positioned over the subclavicular region. Deconvolution analysis was carried out between the blood clearance curve as input function and the activity time curve from each kidney and (kidney minus pelvis) region. The resulting impulse functions were corrected for the contribution from non-filtered (blood background) activity. The areas under the corrected curves were then used as an index of transit time of tracer through the corresponding region of interests. The index for the parenchymal region (Ap) in expressed in "parenchymal transit time units" using an empirical scaling factor.

Results

Radiologically, of 20 cases studied, 11 were diagnosed as having obstruction, in 7 cases no obstruction was thought to be present and in 2 cases the result of the investigation was equivocal. Of the 5 radiological features examined, only 1, increased dilatation of the renal pelvis after frusemide, was common to all 11 obstructed cases. The degree of calyceal dilatation was often difficult to assess when dilated calyces were overlying the renal pelvis. Contrast dilution within the renal pelvis following frusemide and the presence of ureteric filling during the examination were inconstant features of obstruction. Pain occurred during 2 of the investigations but was not a reliable diagnostic feature. In all 11 obstructed cases the percentage increase in renal pelvis size 15 min after frusemide exceeded the renal pelvis size 20 min after contrast but before frusemide by at least 22% (range 22-123%, mean 64·8%). In none of the unobstructed cases did the change in renal pelvis size after frusemide exceed 22% (range −15·5-+22%).

Pressure/flow studies were performed in 16 cases and urodynamic evidence of obstruction was found in 7. There were 2 cases with equivocal results, in both of whom a pressure rise occurred but then a plateau was reached at levels below that which were regarded as diagnostic of obstruction.

Renography was performed in all 20 patients but gamma camera information is not available in 2 because of computer failure. On conventional renography 8 cases were diagnosed as being obstructed, 11 showed a mixing phenomenon and in 1 case with very poor renal function in a solitary kidney the result was equivocal.

Comparison of Results

The correlation between pressure/flow studies and radiological results is shown in Fig. 1. The percentage change in renal pelvis size after frusemide is plotted against parenchymal transit time units. All those with urodynamic evidence of obstruction showed an increase in renal pelvis size after frusemide of more than 22%. There is only one case in whom there was no urodynamic evidence of obstruction yet in whom there was an increase of more than 22% in the size of the renal pelvis after frusemide. These results show that there is good correlation between pressure/flow studies and the change in renal pelvis size after frusemide during high-dose intravenous urography.

Although the dividing line between obstructed and unobstructed cases in terms of parenchymal transit time units is not absolute there is clearly an association between obstruction and parenchymal transit time units. The majority of obstructed cases showed a level greater than 115 Ap.

The correlation between renal function and parenchymal transit time units is shown in Fig. 2. 4 cases diagnosed radiologically and urodynamically as being obstructed showed normal renal function, but the parenchymal transit time unit values for all four cases were greater than 115, the level which seems to differentiate best between obstructed and unobstructed cases diagnosed radiologically and urodynamically.

Discussion

This study indicates that high-dose intravenous urography combined with diuresis provides evidence of renal obstruction which can be quantified. This information correlates well with the results derived from antegrade pressure/flow studies. Since the diuretic IVU is less invasive and since it does not depend for its performance on a difficult puncture technique we believe that this may be the investigation of choice in the assessment of obstructive uropathy.

Interpretation of the gamma camera renographic data is more complex and will be the subject of further study and future reports. In this series the diagnosis of obstruction by conventional renography was unreliable because those showing a mixing phenomenon fell into both the normal and obstructed groups as diagnosed radiologically and urodynamically. Analysis of the gamma camera renogram in those with this mixing pattern enabled the mixing group to be divided into those with obstruction and those without using the criterion that those with over 115 parenchymal transit time units were obstructed. The combination of standard renography combined with deconvolution analysis of the gamma camera renogram gives a good correlation with other techniques (Tables I and II).

It is suggested that measurement of the change in renal pelvis size during high-dose intravenous urography with a diuretic is as reliable as pressure/flow studies in diagnosing an obstructive uropathy. Standard renography combined with deconvolution analysis gives a good separation between those with obstructive nephropathy requiring surgical correction and those whose obstructive uropathy is not causing obstructive nephropathy.

Summary

In 20 patients with pelvi-ureteric junction obstruction the results of quantification of the change in renal pelvis size during high-dose intravenous urography with a diuretic, pressure/flow studies,

Table I

Correlation between Pressure/Flow Studies and Gamma Camera Renography with Deconvolution

		Pressure/flow studies		
		Obstructed	Failed	Normal
Standard renography and deconvolution analysis				
Obstructed	12	7	3	2
Normal	6	0	0	6

Table II

Correlation between Radiological Studies and Gamma Camera Renography with Deconvolution

		High-dose IVU frusemide	
		Obstructed	Normal
Standard renography and deconvolution analysis			
Obstructed	12	10	2
Normal	6	0	6

standard renography and deconvolution analysis of the gamma camera renogram have been compared.

The results of high-dose intravenous urography and pressure/flow studies correlated well. Renography was unreliable in diagnosing obstruction unless deconvolution analysis of the gamma camera renogram was used to differentiate those showing an obstructive uropathy from those with an obstructing nephropathy.

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The Authors

H. N. Whitfield, MA, FRCS, Senior Urological Registrar.
K. E. Britton, MSc, MD, MRCP, Consultant in Charge of Nuclear Medicine.
I. Kelsey Fry, DM, FRCP, FRCR, Consultant Radiologist.
W. F. Hendry, ChM, FRCS, Consultant Urologist.
C. C. Nimmon, BSc, Senior Physicist.
P. Travers, FRCR, DRACR, Consultant Radiologist.
J. E. A. Wickham, MS, FRCS, Senior Consultant Urologist.

Requests for reprints to Mr J. E. A. Wickham, St Bartholomew's Hospital, West Smithfield, London, E.C.1.

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Radionuclide Cystography in the Management of Vesico-ureteric Reflux

D. L. ROTHWELL and A. R. CONSTABLE
Auckland Hospital, Auckland, New Zealand, and Institute of Urology, London

Children with urinary infection and vesico-ureteric reflux unrelated to neuropathic bladder or urethral obstruction are usually investigated with intravenous urograms and micturating cysto-urethrograms. Thus, whatever the course of their clinical management (Williams, 1971; Smellie, 1974; Williams, 1974; Govan, 1975; Manley, Neuman and McAlister, 1976) these children may be exposed to a considerable radiation dose during the course of diagnosis and treatment.

During the last few years radionuclide cystography (R.N.C.) has proved to be a sensitive and accurate alternative to the radiographic investigations having the distinct advantage of considerably less radiation exposure (Conway *et al.*, 1972; Blaufox and Freeman, 1973; Conway *et al.*, 1974; Servadio, Nissenkorn and Baron, 1974).

We have investigated 100 patients for reflux by means of direct (per catheter) R.N.C. and used a recent micturating cystourethrogram (M.C.U.) to assess the accuracy of a very simple gamma camera technique.

Materials

The radionuclide used was ^{99m}Tc pertechnetate, a readily available radionuclide normally used in fairly large quantities for routine imaging procedures. No pharmaceutical preparation is necessary and the required amount of activity is delivered straight from a sterile technetium generator into the sterile saline of a calibrated giving set.

The gamma camera used for all patients in this series was the Nuclear Enterprises Mk III with a resolution of about 1·2 cm and a field uniformity of $\pm 15\%$. No data storage or processing equipment was used and a storage oscilloscope, combined with "Polaroid" photography, was used to display and record reflux when it occurred.

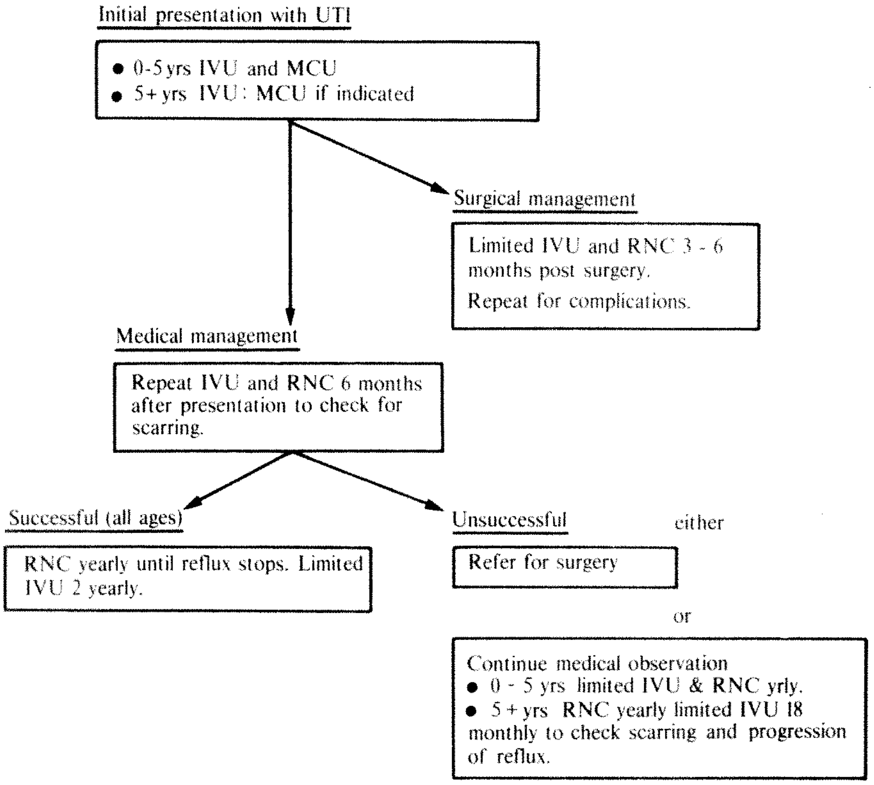
Method

The patient voided, was catheterised, and then lay comfortably on a special nylon mesh imaging couch, with the gamma camera immediately underneath. Saline was instilled into the bladder under low pressure by drip infusion, the first 150 ml (and more recently the first 50 ml) containing 0·5 mCi of ^{99m}Tc pertechnetate. While the bladder was filling the image of the renal area was continuously monitored on the storage oscilloscope and simultaneous Polaroid exposures were obtained from the display oscilloscope. When the bladder was full, the catheter was withdrawn and the patient was placed on a commode with the camera directly behind. Visual monitoring and photography continued during micturition—an obvious advantage of the method. Fluoroscopy during an M.C.U., in the not uncommon event of difficulty in beginning to void, can often result in an undesirably high level of radiation exposure.

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

Table I

Suggested Protocol for treating Children with Urinary Tract Infection



- 0-5 yrs IVU and MCU
- 5+ yrs IVU: MCU if indicated

Limited IVU and RNC 3 - 6 months post surgery.

Repeat for complications.

Repeat IVU and RNC 6 months after presentation to check for scarring.

RNC yearly until reflux stops. Limited IVU 2 yearly.

Refer for surgery

Continue medical observation
- 0 - 5 yrs limited IVU & RNC yrly.
- 5 + yrs RNC yearly limited IVU 18 monthly to check scarring and progression of reflux.

When possible, the residual urine volume was measured by the method described by Strauss and Blaufox (1970). The count rate over the bladder region was noted before voiding (C_0) and again after voiding (C_r). The total volume voided (V) was measured and the residual volume (V_r) was then calculated:

$$V_r = \frac{VC_r}{(C_0 - C_r)}.$$

Inaccuracies and complications may well occur in the presence of reflux, but the figure obtained will usually be of clinical value, even when it is derived from a return of renal activity into the bladder after complete emptying.

Radiation Dosimetry

The radiation dose to the bladder during R.N.C. will depend on the amount of radioactivity and the duration of the investigation. Conway *et al.* (1972) have estimated this dose to be between 53·2 and 63·8 mrad $\text{mCi}^{-1}\ \text{h}^{-1}$ depending on the method chosen for the calculation. The radiation dose to the gonads and to the whole body will be correspondingly small. The normal duration of the investigation is about 30 min and we normally use 0·5 mCi for children which results in a radiation dose to the bladder of about 15 mrad. In contrast to this, the radiation dose received during M.C.U. can range between a few hundred mrad and several rad (Fendel, 1970).

Table II

Exact correlation		65
M.C.U. positive only		19
Lower ureteric reflux	10	
Unilateral reflux	7	
Bilateral reflux	2	
R.N.C. positive only		12
M.C.U. not done	2	
Unilateral reflux	9	
Bilateral reflux	1	
R.N.C. failure		2
Not valid for comparison		2
Total		100

Results

The results obtained are consistent with those reported by other workers (Conway *et al.*, 1972; Blaufox and Freeman, 1973; Conway *et al.*, 1974; Servadio *et al.*, 1974) (Table I). In most cases the M.C.U. had been performed within a few days of the R.N.C. though in some cases comparisons were made with studies performed up to one year earlier.

The R.N.C. was satisfactory for detecting the grosser forms of reflux and our results confirm that lower ureteric reflux cannot normally be detected by R.N.C. (Bailey *et al.*, 1976), though it can sometimes be observed in adult patients (Fig. 3). This lack of sensitivity in demonstrating the

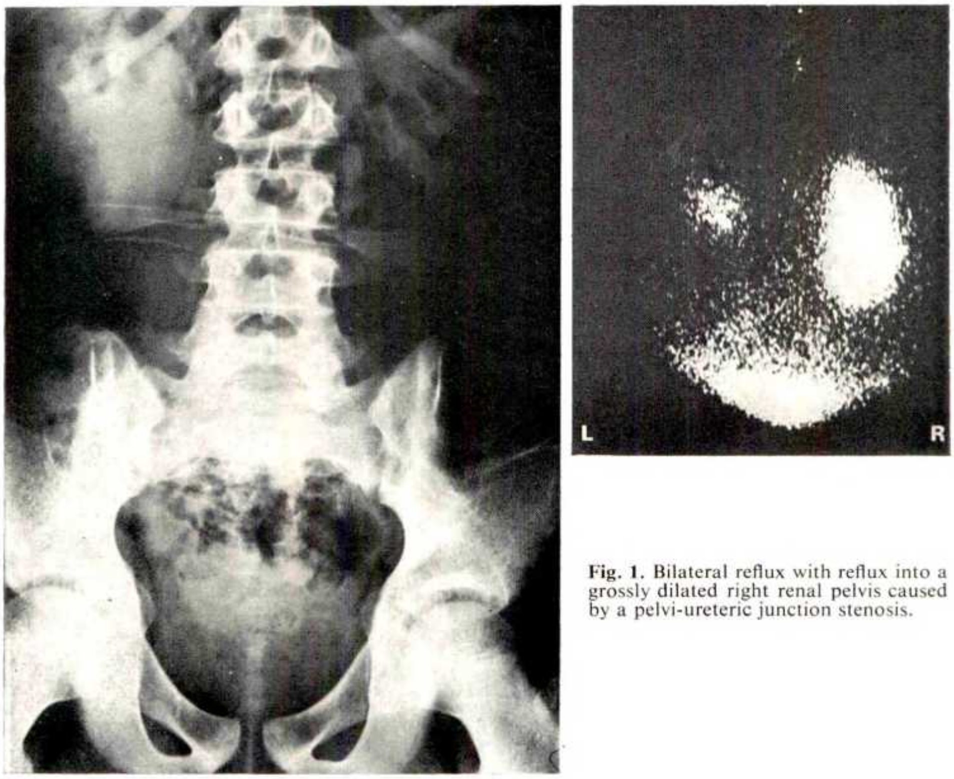


Fig. 1. Bilateral reflux with reflux into a grossly dilated right renal pelvis caused by a pelvi-ureteric junction stenosis.

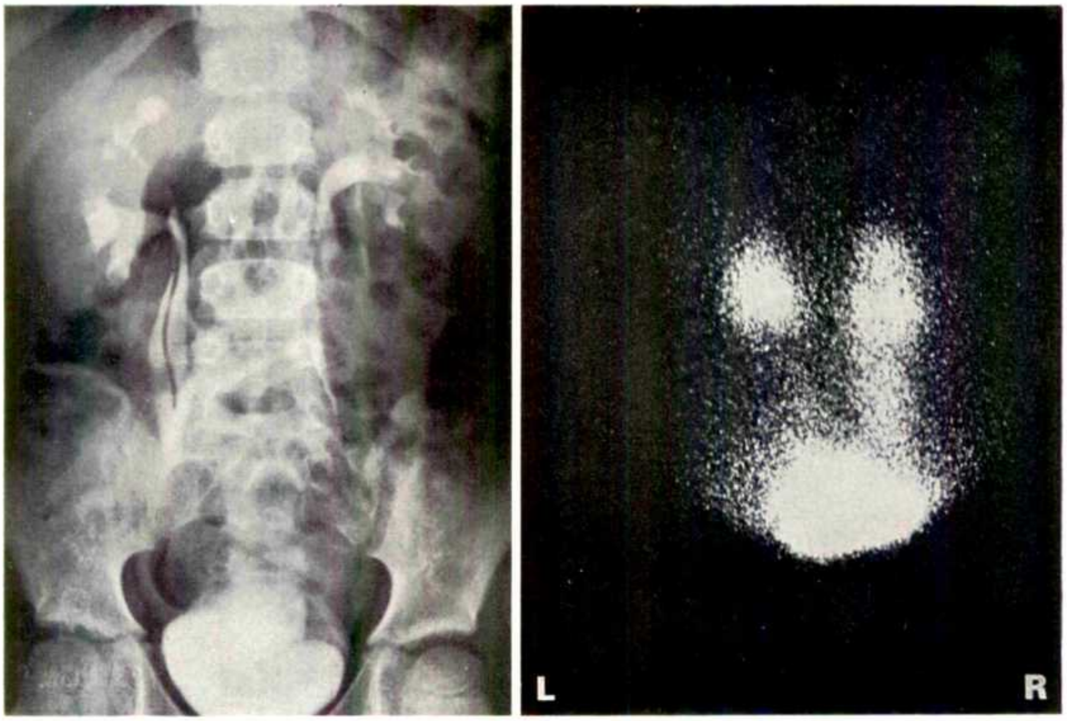


Fig. 2. Bilateral reflux showing reflux into both moieties of a right-sided duplex kidney.

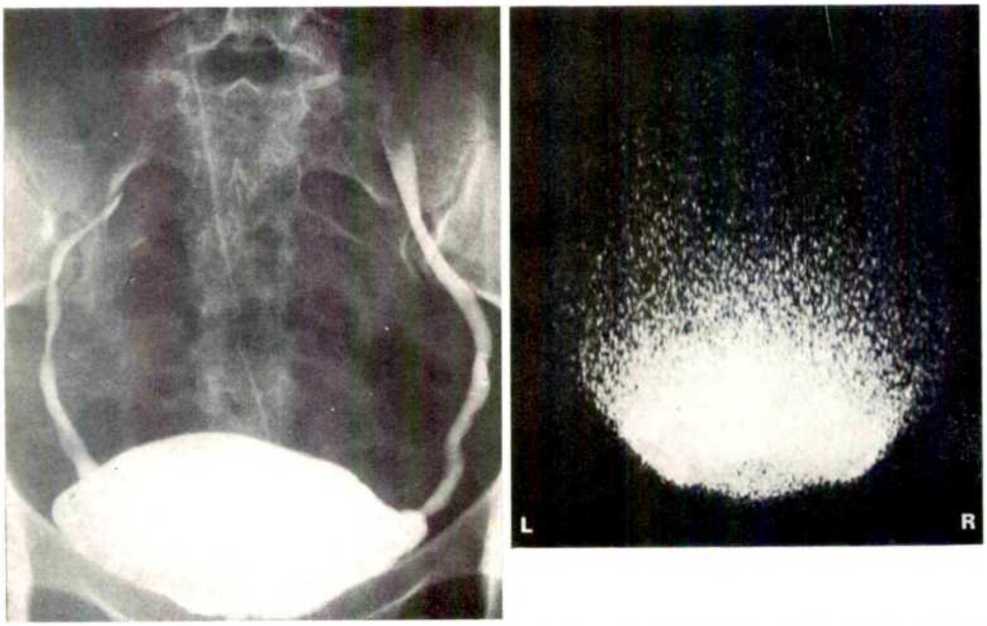


Fig. 3. Bilateral minimal reflux in an adult patient. The fleeting appearance of reflux can often be observed on the storage oscilloscope but can be difficult to photograph during the investigation.

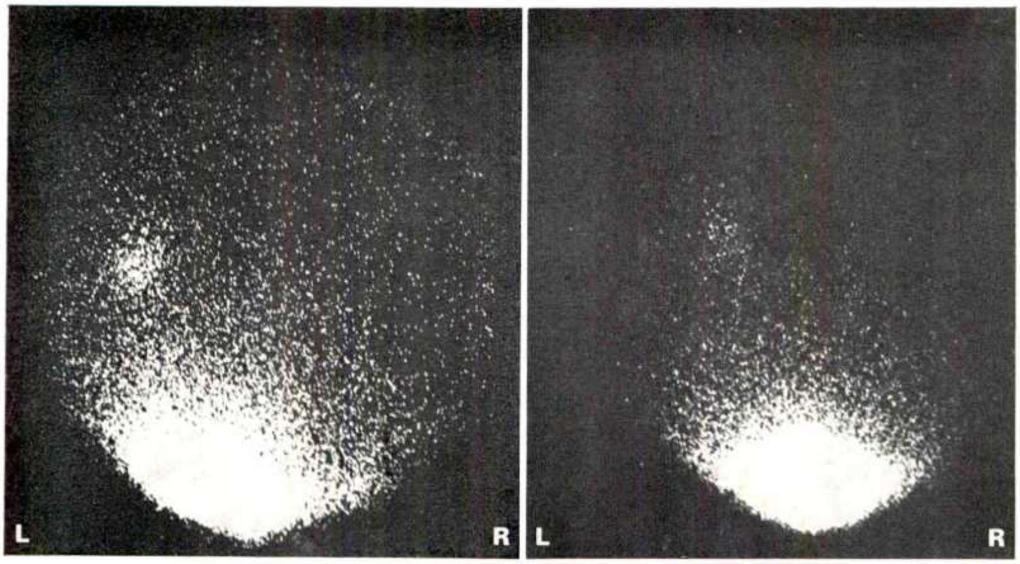


Fig. 4. R.N.C. results in a 10-year-old girl with vesico-ureteric reflux and recurrent infection. (left) Reflux to the left side at the start of antibiotic treatment. After finishing a course of antibiotics urine culture was sterile and R.N.C. was repeated (right) and demonstrated considerably less intense reflux.

presence of activity in the lower part of the ureter is accounted for by the shielding effect of the bladder activity and the shorter ureteric length in children.

The occasional discrepancy between the results of R.N.C. and M.C.U. may well be a consequence of the inherent intermittency of reflux known to occur with some children. Many children who have recurrent infections probably do not have significant reflux at every voiding while the urine is sterile (Fig. 4). Although other workers have referred to spontaneous cessation of reflux (Stephens and Lenaghan, 1962; Smellie and Normand, 1968; Reischauer, Olbing and Stroetger, 1968), it may be that recovery is not permanent (Williams, 1971).

Discussion

There is considerable controversy about the effects of reflux, infection and intrarenal reflux in causing renal damage, resulting in some uncertainty in the management of children with recurrent urinary-tract infection and reflux. We suggest a protocol for the investigation and management of these children which is aimed at reducing the amount of radiation to a minimum and at the same time allowing an accurate assessment of the patient at presentation and follow-up (Table II).

At initial presentation all children between the ages of 0 and 5 years should have a full intravenous urogram (I.V.U.) and M.C.U. Over the age of 5 years, an M.C.U. is indicated if the child has recurrent infection despite a normal I.V.U. An abnormal I.V.U. calls for an M.C.U. at any age. If the M.C.U. is negative but there is a clinical suspicion of pyelonephritis, R.N.C. is indicated while the child is infected, provided there is adequate antibiotic cover.

Some workers (Rolleston *et al.*, 1974; Ransley and Risdon, 1975) believe that intrarenal reflux usually stops after the age of 5 years and that renal scarring occurs before this age. Our own clinical experience has shown good evidence of renal damage occurring in children aged more than 5, together with the possibility of progressive ureteric dilation, kinking and obstruction. We believe that continual observation is therefore required.

The surgical management is usually straightforward and 3 to 6 months after the anti-reflux procedure an I.V.U. and R.N.C. should be performed to check for obstruction and reflux. If complications from surgery arise (*e.g.* contralateral reflux), then further R.N.C.s may be performed.

If it is decided to treat the patient medically an I.V.U. together with an R.N.C. should be performed 6 months after the first infection, to see whether damage occurred at this initial episode (Lenaghan *et al.*, 1976). If the medical management is successful and the patient remains well, it is advisable for follow-up to be continued until the reflux is seen to stop, as it may well do as a result of the maturation of the vesico-ureteric junction (Williams, 1971). In the event of unsuccessful medical treatment, for whatever reason, the patient may be referred for surgery or continue to be observed closely.

It is well-known that there is a close relationship between vesico-ureteric reflux, infected urine and intrarenal reflux producing renal damage and renal scarring. It is difficult to demonstrate intrarenal reflux (I.R.R.) using present-day techniques, but a preliminary investigation has shown that it might be possible during R.N.C. Using a pig kidney *in vivo*, previously shown to have I.R.R., isotope injected into the renal pelvis via the ureter appeared in the renal cortex with considerably greater concentration in the regions of scarring. There exists the possibility that there will be high levels of vascular activity in the presence of intrarenal reflux and some of our animal investigations have already shown this to be so. Further investigations are in progress in the hope that we may be able to show reliably the presence of I.R.R. in the clinical situation.

Summary

Direct radionuclide cystography in 100 patients has been shown to be a useful investigation in the diagnosis and management of reflux and a valuable complement to radiographic methods; it may well have a place in the detection of reflux in the infected patient.

The advantages include low radiation exposure, an accurate measurement of residual urine volumes, simplicity of technique and the use of materials and equipment that have in recent years become increasingly available for routine investigation.

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The Authors

D. L. Rothwell, FRACS, Urological Tutor, Auckland Hospital.
A. R. Constable, MSc, MhistP, Senior Lecturer in Medical Physics, Institute of Urology.

Requests for reprints to A.R.C. Institute of Urology (University of London), 172 Shaftesbury Avenue, London, WC2H 8JE.

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Ureteric Advancement in the Treatment of Reflux

PETER F. JONES
Royal Aberdeen Children's Hospital

During the development of surgery for ureteric reflux a number of techniques were described. Some proved to be unsatisfactory, but others of considerable value were not widely adopted. One of the latter is ureteric advancement, which was introduced by Williams, Scott and Turner-Warwick in 1961. A different intra-vesical technique was described by Hutch in 1963, but there are few reports of the results of these procedures. A ureteric advancement operation has been used regularly in this hospital since 1966 and continues to give good results. This paper reports the indications for this procedure, the technique and the results obtained.

Patients

Each year some 100-120 children are fully investigated in the Urological Clinic and between 10 and 12 of them require surgery for ureteric reflux which is not associated with major outlet obstruction. The criteria used to select patients for surgical correction are:

(1) Severity of reflux. Reflux which causes marked distension of the ureter and severe clubbing of calyces is generally considered an indication for surgery in itself, not least because of the continued hydraulic pressure effects on the kidney. When distension and clubbing are less severe, then account is also taken of.

(2) Age. Reflux is regarded more seriously in young children because they have to live with it longer before spontaneous improvement is likely.

(3) A normal intravenous pyelogram is an encouragement to surgery in so far as it is hoped to preserve a normal kidney. In particular, advancement was used in a number of children to control moderate reflux and so to protect a normal kidney, when the opposite kidney had already been affected by severe reflux and infection.

(4) Normal ureteric orifices seen at cystoscopy generally encourage a conservative attitude and incompetent-looking orifices are more likely to be operated upon.

(5) 49 of the 58 children having an advancement had a persistent urinary infection before operation.

The application of these criteria led to 91 children being selected for surgical treatment during 1966-1975 (Table I).

The decision to use either an advancement or a tunnel procedure was based largely on the appearance of the ureters in the intravenous urogram (without compression). In general, when the lower ureter appeared to be normal in calibre an advancement was done, and when the ureter was dilated a Politano-Leadbetter re-implantation operation was chosen. This decision was occasionally altered in the light of the findings at operation. An advancement was done on a total of 84 ureters and a Politano-Leadbetter operation on 59 ureters (Table I). Of the children having an advancement, 40 were girls and 7 were boys: 22 were under 5 years of age.

Operative Technique

The operation is performed entirely within the bladder. The medial and lateral edges of the ureteric orifice are picked up with two stay sutures of 4/0 silk and the orifice is circumcised, using

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small blunt-nosed scissors. Then sharp dissection is used to separate the ureter from its attachments to the bladder wall and to the trigone, until it is completely free: when this process is complete, 1·5-2·0 cm of ureter can be easily drawn into the bladder. This dissection almost always reveals a substantial defect in the bladder wall, even though the mobilisation has always been done by cutting close to the wall of the ureter. This defect—which can be 2 or 3 times the diameter of the ureter—is narrowed by placing one or two 3/0 chromic catgut sutures through the bladder wall, below the emerging ureter, so that the bladder encloses but in no way constricts the ureter.

A shallow trench is next cut across the trigone with scissors, aiming towards the internal urinary meatus. This trench must be 1·5 cm long and can be longer, depending on how far the ureter can easily stretch and on the size of the trigone. 3 or 4 sutures of 4/0 collagen are used to stitch the margins of the ureteric orifice to the distal end of the trench. No attempt is made to cover the ureter with mucosa but 1 or 2 anchoring sutures are usually passed between the mucosa at the site of the original ureteric orifice and the ureteric wall just as it enters the bladder. No ureteric splints or catheters are needed and a good efflux is nearly always seen as the operation is being completed.

Although some have found the trigone too small to carry out this operation successfully, this has rarely been our experience. However, in 4 children the modification suggested by Cohen and illustrated by Williams (1975) has proved a good alternative in these circumstances.

Initially a bladder neck myotomy was performed at the end of the operation but this has only been done twice in the last 8 years.

Follow-up

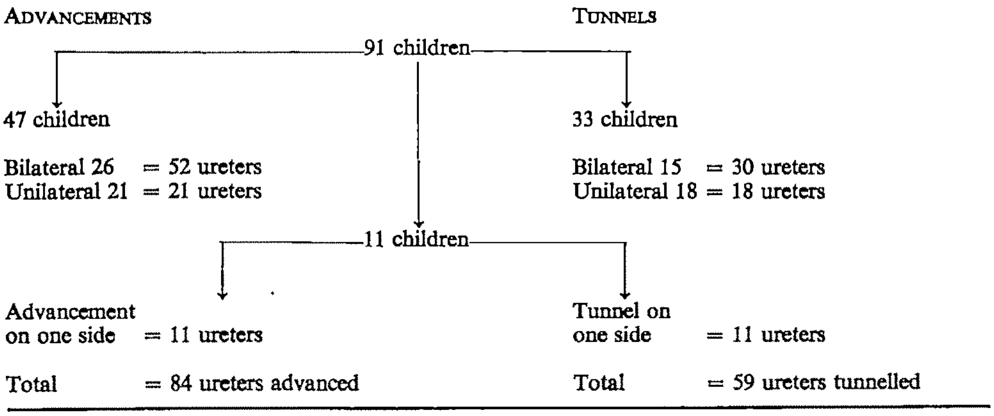
All the 58 patients who had an advancement were followed for 1 year and 50 children have been seen more than 2 years after operation. An intravenous urogram has been done 4-6 months after operation: most patients have had a micturating cystogram at the same time although this was deliberately omitted in a few young children who had been upset by the original cystogram. Thereafter the children are seen twice a year and a fresh intravenous urogram done every 3 years to check renal growth.

Results

The only examples of failure to correct reflux are 2 children who show a trace of medium in the lower part of a ureter (but 9 young children did not have a postoperative cystogram) Table II.

Table I

Patients requiring Surgery for Ureteric Reflux during 1966-1975


ADVANCEMENTS
TUNNELS
91 children
47 children
33 children
Bilateral 26 = 52 ureters
Unilateral 21 = 21 ureters
Bilateral 15 = 30 ureters
Unilateral 18 = 18 ureters
11 children
Advancement on one side = 11 ureters
Tunnel on one side = 11 ureters
Total = 84 ureters advanced
Total = 59 ureters tunnelled

It therefore appears that, provided only ureters of normal calibre are advanced for 1·5 cm, this operation is a reliable one in correcting reflux. It also appears to be a safe operation in so far as there is no example of any ureteric obstruction developing. The 3 patients who had a normal pyelogram preoperatively but who have since developed signs of pyelonephritis are children in whom both reflux and infection have been overcome: it seems likely that these kidneys were scarred at the time of operation and this has become evident as they have grown. Postoperative cystoscopy has been undertaken in 10 children and the appearances of the advanced ureters and orifices are very satisfactory.

The urine cultures of these children fall into 3 groups. There are those who have kept a sterile urine for some time, without medication (32/58), those who require co-trimoxazole (or occasionally another urinary antiseptic) to keep the urine sterile (14/58) and the remainder who sometimes have a significant urine culture but suffer no symptoms attributable to it.

1 girl who was referred at the age of 6 with marked bilateral pyelonephritis and who had bilateral advancements in the hope that this would assist control of infection slowly deteriorated and died in renal failure 2 years after operation. Another girl who had a bilateral advancement aged 6, when her left kidney showed marked pyelonephritic changes, required a nephrectomy at 16 years of age: reflux was abolished but the left kidney never grew and became largely functionless and there was a modest rise of blood pressure. Compensating growth of the normal right kidney has been excellent.

A girl aged 11 with marked bilateral reflux and a small scarred functionless right kidney had a right nephro-ureterectomy and left advancement. She recently went through a normal pregnancy at the age of 20 and the post-delivery IVP looks normal.

Discussion

The operation of ureteric advancement described here appears to have several advantages:

1. The technique is simple and the operation is quickly completed.
2. If there is strict adherence to the rule that the ureter must be of normal calibre then it appears that reflux is reliably abolished.
3. An outstanding advantage is that, so far, no case of postoperative ureteric obstruction has occurred. This means that it is safe to use advancement to protect a refluxing but otherwise normal kidney when the contralateral kidney is already pyelonephritic. It also encourages the surgeon to operate on young children who have appreciable bilateral reflux up to normal kidneys.

This absence of obstruction contrasts with my own experience and that of others (Scott, 1977) after performing the Politano-Leadbetter operation. Even with the greatest care over all the details of the operation, 5 of the 59 ureters in this series which were re-implanted by this technique developed postoperative obstruction and had to be re-explored. This complication may be partly

Table II

Results of the Ureteric Advancement Operation

Follow-up of 84 Advancements (All > 1 year, 71 > 2 years)		
IVP normal before and after	48	
Pyelonephritic changes before and after	27	(1 Nephrectomy) (16 Kidneys growing) (1 Late death)
IVP normal before, P/N after	3	
?P/N before, normal after	6	
Recurrence of reflux	2	(Minor)
Postoperative hydro-ureter	0	(5/59 Tunnels)

due to the fact that the Politano-Leadbetter procedures were selectively done on dilated ureters but the complete freedom from obstruction in the advancement series is still an important point.

The technique described here differs in several respects from that described by Williams *et al.* (1961) and by Hutch (1963). The details of the operations which they illustrate suggest that the ureteric orifice will not be advanced in the bladder by more than 1·0 cm and perhaps by not so much as that. Neither of these papers refers to the large defect in the bladder wall which is revealed by more extensive dissection and which, if uncorrected, means that the ureters have no support at their point of entry into the bladder. This defect is easily corrected and may contribute appreciably to the success of the operation.

The operation described by Glenn and Anderson (1967) resembles the operation described here in many ways but the direction of the advancement must make it difficult to perform a bilateral operation: Cohen's modification, taking the ureters transversely above the trigone, seems a better technique.

Tanagho (1970) has reviewed the considerable advantages of an advancement type of procedure and he also stresses the protection this operation provides against obstruction. His reserve about the usual advancement operation is that it preserves the lower end of the ureter, which Tanagho prefers to remove. If the operation is confined, as in this series, to ureters of normal calibre this objection does not seem to be a major one, as judged by the results reported here.

Williams and Eckstein (1965) found that their advancement operation had prevented reflux in 12 out of 14 ureters, although 1 had developed postoperative obstruction. Hutch, Smith and Osborne (1968) reported on the results of 83 operations by the Hutch (1963) technique and found reflux had ceased in 72, but there were 3 ureters which became obstructed. Possibly, therefore, the modifications in the advancement operation which are described here are helpful.

By selecting our patients we have used advancement on a particularly favourable group of patients. However, many of these children had already suffered appreciable renal damage and many had not done well during a trial of medical treatment. It is of considerable value to be able to offer this group of patients an effective operation which is generally free of complications, and we have been repeatedly impressed by the spontaneous comments of parents on the greater well-being and growth which they see in their children after ureteric advancement.

Summary

Among 91 children requiring surgical correction of major ureteric reflux, 58 had 1 or 2 ureters treated by an advancement operation. This proved to be highly effective in preventing further reflux and in no case did any ureteric obstruction develop. The indications for choosing this operation, and a suitable operative technique, are described.

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The Author

Peter F. Jones, MChir, FRCS, FRCSE, Consultant Surgeon.

Address for reprints: Royal Aberdeen Children's Hospital, Cornhill Road, Aberdeen AB9 2ZG.

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The Unstable Bladder—Fact or Artefact?

P. D. RAMSDEN, J. C. SMITH, J. M. PIERCE and G. M. ARDRAN
The Department of Urology and the Nuffield Institute for Medical Research, Oxford

From the time of Mosso and Pellicani (1882) the cystometrogram, its interpretation and its clinical significance in evaluating problems of the lower urinary tract has been the subject of controversy.

In recent times the recognition of the phenomenon of spontaneous and induced bladder instability and the clinical implication of this finding in patients with urge incontinence (Bates, 1971), stress incontinence (Arnold *et al.*, 1973) and persisting symptoms after prostatectomy (Turner Warwick *et al.*, 1973) gives added importance to this debate.

However, few studies have been published to determine the consistency of this abnormality and there remains a doubt that it may be an artefact related to the unphysiological conditions of cystometry, particularly the rapid rates of filling usually employed.

In this study several cystometrograms have been performed at each examination and the effect of filling at different rates and in different positions on the bladder capacity and incidence of instability has been assessed. This has included pressure measurements carried out during normal filling of the bladder, the rate being determined by the renal output of urine.

Patients

The patients studied were a highly selected group referred for urodynamic assessment to the Radcliffe Infirmary, Oxford, over a 16-month period.

Preliminary clinical examination, urine culture and IVU were carried out on all patients. Urodynamic assessment comprised filling cystometrograms in the supine and erect positions, measurement of urethral profile and micturating cine-cystourethrography.

Method

Bladder and rectal pressures were recorded as the bladder was filled with saline at room temperature at a constant rate of 25 or 100 ml per min.

Throughout, the patient was asked to hold the urine and filling was terminated when the patient felt uncomfortably full or when urinary leakage began.

The patient was then asked to cough and strain and elevated to the vertical and asked to cough and strain again. A further cystometrogram was carried out in the erect position, sitting in the female and standing in the male.

In 12 patients, all of whom demonstrated instability at their initial examination, a further examination was performed on a separate occasion with physiological bladder filling: bladder and rectal pressures were measured as the bladder slowly filled with urine.

Instability was considered present if the desire to void was accompanied by an involuntary detrusor contraction. At the end of the examination the bladder was emptied and this volume added to any urine leaked, so that bladder capacity and rate of filling could be calculated.

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

Results

The results of 395 cystometrograms, carried out during the course of 179 separate examinations on 100 patients were analysed. Where several examinations on the same patient had been carried out and the patient had had intervening treatment, only cystometrograms carried out at the same examination were compared.

The ages of the patients ranged from 6 to 82 years. 61 were female and 39 male.

Of the 100 patients, 62 were demonstrated to have an unstable bladder, and these comprised 36 with idiopathic bladder instability and 26 with secondary bladder instability (Table I).

No differences were observed between patients with idiopathic bladder instability and patients with secondary bladder instability, when each group was analysed separately, and therefore subsequent reference will be made only to the total group of patients with unstable bladders, irrespective of aetiology.

The 38 patients with stable bladders included 20 who had entirely normal pressure flow studies (Table II).

The Effect of Filling Rate

Bladder capacities recorded at consecutive cystometrograms, filling initially at 100 ml per min supine and then at 25 ml per min supine, were compared (Fig. 1). No significant difference in bladder capacity was observed between fast and slow filling in both patients with stable bladders ($t = 0{\cdot}64$) and patients with unstable bladders ($t = 0{\cdot}35$).

Again comparing filling at 100 and 25 ml per min, in those patients in whom one of the cystometrograms showed spontaneous contractions on filling, on 88% (30/34) of occasions, the other cystometrogram also showed spontaneous contractions on filling (Fig. 2).

14 patients, all of whom showed spontaneous contractions on filling at 100 ml per min were investigated on a subsequent occasion when bladder pressure was measured as the bladder filled "physiologically'. There was a mean increase in capacity of 66 ml filling physiologically, but the standard error of the mean was high (45·4) and this change did not reach significant levels ($t = 1{\cdot}45$).

86% or 12/14 showed spontaneous contractions on filling at both 100 ml per min and "physiologically" (Fig. 3).

The Effect of Filling Position

Bladder capacity at 100 ml per min supine was compared with 100 ml per min erect—sitting in the female and standing in the male (Fig. 4). No significant difference was observed in the patients

Table I

Patients with an Unstable Bladder

Group 1.	Idiopathic instability		36
Group 2.	Secondary instability		
	Associated neurological abnormality	10	
	Outflow obstruction	11	
	Others	5	
		—	26
			—
			62

Table II

Patients with a Stable Bladder

Group 3.	Normal urodynamics		20
Group 4.	Others		
	Outflow obstruction	4	
	"Hypersensitive bladder"	3	
	Interstitial cystitis	6	
	Atonic bladder	2	
	Others	3	
		—	18
			—
			38

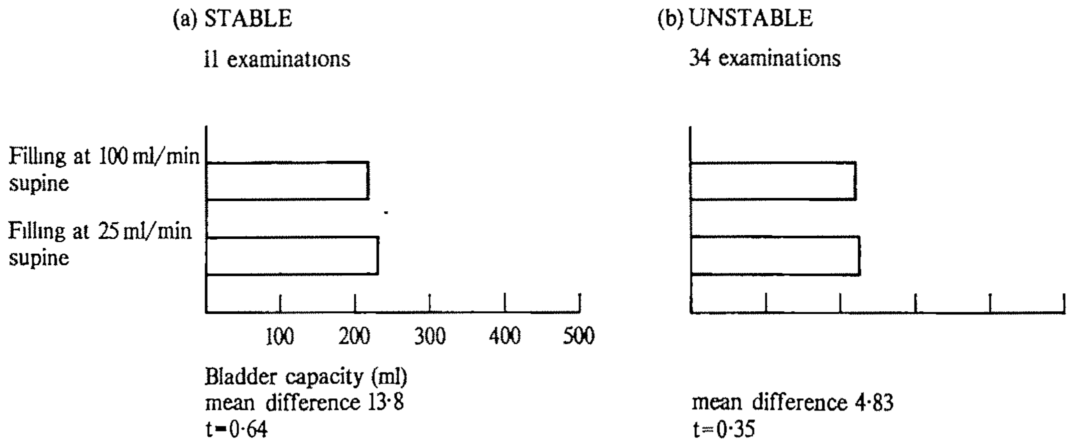


Fig. 1. Comparison of mean bladder capacities filling consecutively at 100 ml/min supine and 25 ml/min supine.

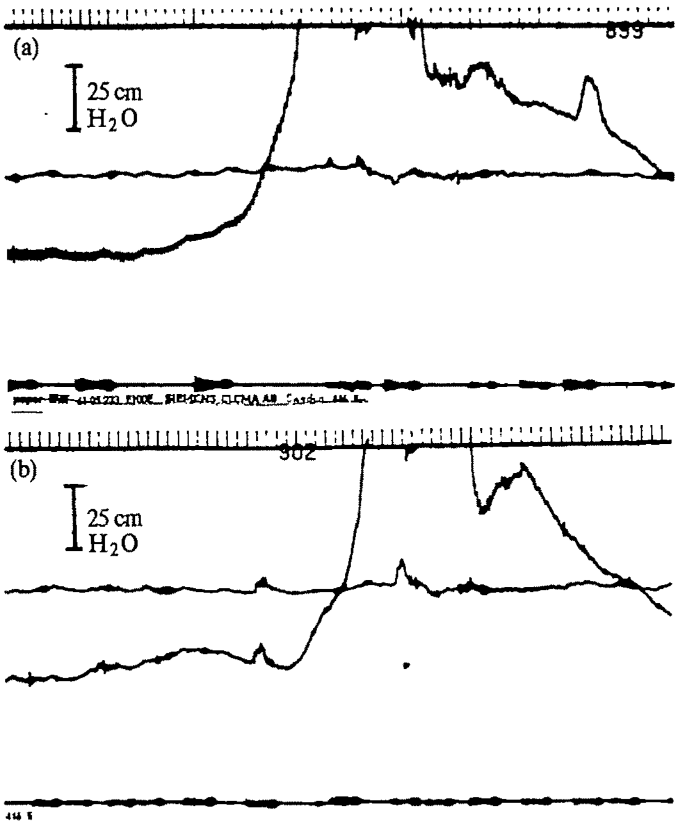


Fig. 2. Consecutive cystometrograms from the same patient (A. T.) carried out at the same examination, each demonstrating bladder instability. (*a*) Filling at 100 ml/min supine; capacity 109 ml. (*b*) Filling at 25 ml/min supine; capacity 69 ml.

with stable bladders, (t = 0·30) but in those with unstable bladders there was a mean capacity decrease of 112 ml on filling erect which was highly significant (t = 5·81, $P < 0{\cdot}001$).

The above results relate to consecutive cystometrograms carried out under different filling conditions. In order to investigate the effect of consecutive filling alone, patients have been filled successively at the same rate (100 ml/min), and in the same position (supine) and the results compared. Bladder capacity was unchanged in both patients with stable bladders (8 examinations, t=0·02) and patients with unstable bladders (23 examinations, t=1·03). In those patients with spontaneous detrusor contractions on filling on 1 of the cystometrograms, this abnormality was also present on the other cystometrogram on 96% (22/23) of occasions.

We have carried out several cystometrograms at each examination but would one cystometrogram at 100 ml per min supine be sufficient? Fig. 5 shows the result of the first cystometrogram at 100 ml per min supine carried out during the course of each examination in those examinations where bladder instability was demonstrated.

Spontaneous contractions on filling were present on 89% of these cystometrograms. If in addition the cystometrogram included both elevation to the vertical and testing for induced contractions, 97% of patients with instability were detected.

For further comparison the result of the first cystometrogram at 100 ml per min erect, carried out during the course of each examination in those examinations where bladder instability was demonstrated, is shown in Fig. 6. 90% showed instability on the filling cystometrogram and when induced contractions are included 98·5% of patients with instability were detected.

These results may give the misleading impression that in the majority of our patients spontaneous contractions were the only manifestation of instability. However, many patients showed both spontaneous and induced contractions. Of those shown to have bladder instability, 71% demonstrated induced detrusor contractions following a cough, strain or change in position, although in only 8% was this the sole expression of instability.

Discussion

We have examined the influence of 2 variables, that of speed of filling and filling position, on bladder capacity and the incidence of spontaneous detrusor contractions.

Turner Warwick and Whiteside (1976) draw distinction between the terms "uninhibited" and "unstable", the former being reserved for patients who develop contractions on supine filling, and in whom the rate of filling may be critical to the distinction between "uninhibited" and "normal". In our study, varying the rate of filling failed to produce significant change in bladder capacity, or in the detection of spontaneous detrusor contractions, and we would be in favour of referring to all patients who show spontaneous detrusor contractions on filling, or induced contractions in response to a sudden rise in intra-abdominal pressure, as having "unstable bladders".

Filling in the erect position, although not influencing the incidence of spontaneous detrusor contractions, in those patients with unstable bladders, did result in a reduction in mean bladder capacity of 112 ml, supporting a similar result previously reported by Warrell and Clow (1974).

Although several cystometrograms were carried out at each examination, in those patients shown to have bladder instability, approximately 90% of patients showed spontaneous contractions on the first filling cystometrogram, whether filling was carried out supine or erect. If the cystometrogram included testing for induced contractions in the vertical position, over 95% of patients with instability were detected on the initial cystometrogram.

These findings differ from those of Arnold (1974) who reported that 58% of patients with instability would not be detected by supine filling alone. Arnold's results were obtained using electronic subtraction of rectal pressure, but in practice we found induced contractions, when present, were obvious and do not believe the addition of this facility would have had a significant influence on our results. This apparent discrepancy may reflect different populations of patients studied, and both studies do confirm that failure to look for induced contractions in the vertical position will result in a proportion of patients with bladder instability remaining undetected.

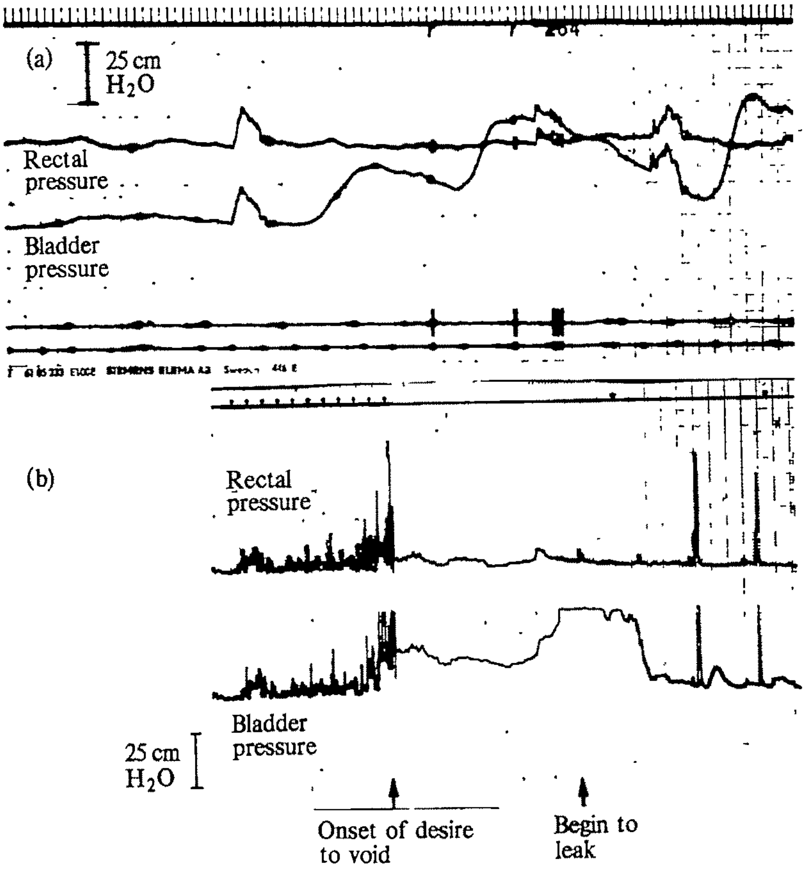


Fig. 3. Two cystometrograms from the same patient (J. B.), each demonstrating bladder instability. (*a*) Filling at 100 ml/min supine; capacity 320 ml. (*b*) Filling "physiologically"; capacity 110 ml; filling time 80 min. Rate of filling 1·38 ml/min.

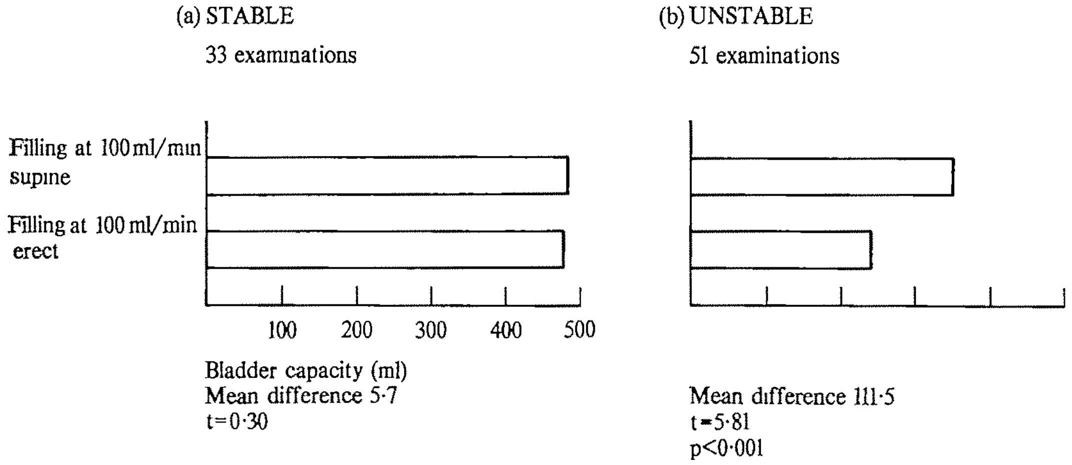
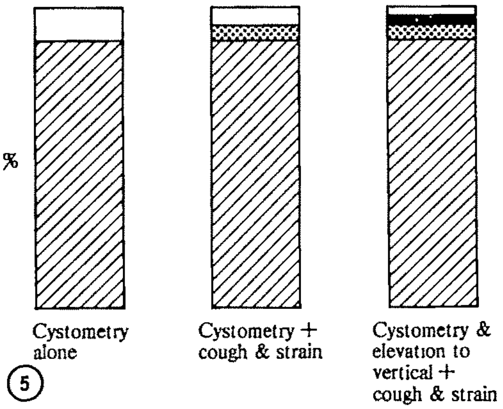


Fig. 4. Comparison of mean bladder capacities filling consecutively at 100 ml/min supine and 100 ml/min erect.



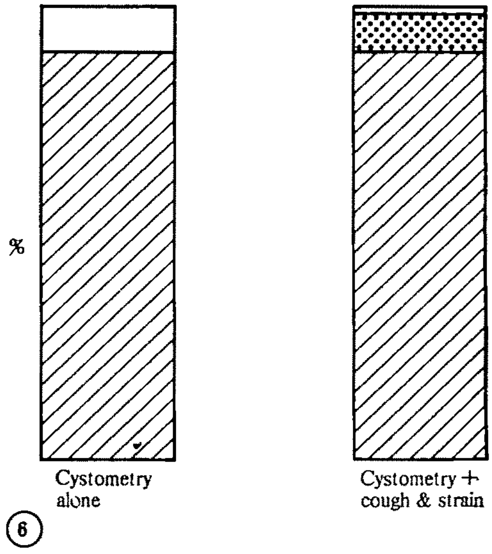


Fig. 5. To detect bladder instability—Would one cystometrogram at 100 ml/min *supine* be sufficient? 105 examinations—59 patients.

Fig. 6. To detect bladder instability—Would one cystometrogram at 100 ml/min *erect* be sufficient? 68 examinations—46 patients.

Conclusion

Bladder instability, defined as an abnormal involuntary detrusor contraction, is a consistent phenomenon under wide variations in technique of cystometry. The observed correlation between instability and symptoms of urgency and incontinence (Farrar *et al.*, 1975) strongly supports our conclusion that it is a naturally occurring phenomenon and not an artefact induced by the technique of investigation. Further evidence is provided by the response of these patients to prolonged bladder distension, where relief of symptoms and conversion to a stable cystometrogram go hand in hand (Ramsden *et al.*, 1976).

Summary

100 patients, referred for urodynamic study, have had several cystometrograms performed at each examination, and the effect of filling at different rates and in different positions has been assessed. This has included pressure measurements carried out during "physiological" bladder filling.

Bladder instability was found to be a highly consistent phenomenon, its detection being independent of filling rate or position of filling.

We wish to thank Miss Penelope Fursdon and Miss Wendy Hills for their excellent technical assistance with the cystometry. We are grateful also to the Department of Medical Illustration, Radcliffe Infirmary, for help with the illustrations, and to Mrs Jean Broadis who has prepared the manuscript.

This work forms part of a Thesis to be submitted (by P. D. R.) to the University of London for the degree of Master of Surgery.

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The Authors

P. D. Ramsden, FRCS, Research Registrar. (now Senior Urological Registrar, General Hospital, Newcastle upon Tyne).

Joe C. Smith, MS, FRCS, Consultant Urological Surgeon, Oxford.

J. M. Pierce, MSc., (Med. Stat.) Departmental Research Assistant, Department of Biomathematics, University of Oxford.

Gordon M. Ardran, MD, FRCP, FFR, Radiologist, Nuffield Institute for Medical Research, University of Oxford.

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Interstitial Cystitis, treated by Prolonged Bladder Distension

M. DUNN, P. D. RAMSDEN, J. B. M. ROBERTS, J. C. SMITH and P. J. B. SMITH
Departments of Urology—Bristol, Bath and Oxford

Interstitial cystitis was first recognised, unwittingly, in 1914 by Hunner, who described the presence of a simple ulcer in the bladders of female patients with long histories of lower urinary tract symptoms. It is an uncommon condition. Kinder and Smith (1958), in reviewing 17,248 registered new patients at St Peter's and St Paul's Hospitals, found the incidence of interstitial cystitis to be 0·23%.

The cause of interstitial cystitis is still unknown. It is possible that it is an auto-immune condition and is due to some upset in collagen metabolism localised to the bladder (Silk, 1970). As the cause of interstitial cystitis is unknown, treatment has to be empirical. Hunner considered local excision of the affected area to be the best form of treatment in severe cases. Many forms of conservative treatment have been tried, including bladder instillation with silver nitrate, Neomycin, potassium iodide, warm boric acid, Chlorpactin and Butazolidin, local injection with saline and heparin (Weaver, Dougherty and Natoli, 1963), Tanderil (Guerrier, Roberts and Slade, 1965) and hydrocortisone, antibiotics, Probanthine, oestrogens, ACTH, systemic cortisone and hydrostatic distension of the bladder under general anaesthesia.

Many operative procedures have also been described, including ileocystoplasty, ileocystoplasty with radical partial cystectomy, caecocystoplasty, colocystoplasty, ureterosigmoidostomy, implantation of intravesical radon seeds and ileal loop conduit. All these procedures involve major surgery with significant morbidity, and although some patients have sustained improvement, the overall results are disappointing and some patients are made worse.

Vesical distension has been used successfully for many years, but the beneficial response has been short-lived, so it was thought that a more sustained remission might be attained by prolonged bladder distension under epidural anaesthesia. We describe the results of 25 patients with interstitial cystitis treated by prolonged bladder distension.

Patients

The patients were considered to have interstitial cystitis according to the following criteria:

1. A history of severe frequency and nocturia, associated with suprapubic pain, often relieved by micturition, albeit transiently; in the presence of a sterile urine and normal excretion urography.
2. The cystoscopic features of small haemorrhagic patches appearing on filling, followed by the development of shallow irregular linear ulcers, commonly in the vault, and a small bladder capacity.

22 (88%) of the patients were female. The age range was from 32 to 80 years with a mean of 65·5 years. The length of history varied from 9 months to 11 years with a mean of 5 years. All the patients had failed to obtain any reasonably sustained symptomatic improvement from conventional treatment.

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

Table I

Frequency

	Frequency of micturition			
	10-30 min	30-60 min	1-2 hours	2-3 hours
Before prolonged bladder distension	9	9	7	–
After prolonged bladder distention	1	3	8	13

Table II

Nocturia

	Frequency of micturition			
	0-2	3-5	6-9	More than 9
Before prolonged bladder distension	1	9	8	7
After prolonged bladder distension	15	5	4	1

Table III

Pain and Urgency

	Before prolonged bladder distension	After prolonged bladder distension
Pain		
Suprapubic	22	6
Urethral	17	5
Urgency		
None	11	22
Moderate	14	3

Table IV

Results of Previous Prolonged Distension

Patient No. 3	1st distension symptom-free 6/12	Now symptom-free 3/12
Patient No. 5	1st distension symptom-free 15/12	Now symptom-free 6/12
Patient No. 6	1st distension symptom-free 4/12	Now symptom-free 9/12
	2nd distension symptom-free 7/12	
Patient No. 7	1st distension symptom-free 7/12	
	2nd distension symptom-free 6/12	Now improved 8/12
	3rd distension symptom-free 7/12	
	4th distension symptom-free 5/12	
Patient No. 9	1st distension symptom-free 7/12	
	2nd distension symptom-free 7/12	Now symptom-free 18/12
	3rd distension symptom-free 10/12	
	4th distension symptom-free 4/12	
Patient No. 12	1st distension symptom-free 5/12	Now symptom-free 7/12

Procedure

Cystometry, as described by Dunn, Smith and Ardran (1974), was performed preoperatively and these studies were repeated again postoperatively. Prolonged bladder distension was carried out after high epidural anaesthetic. Each patient was cystoscoped and the bladder capacity measured. An 18 Ch Latex catheter with a condom or toy balloon securely tied to its end was introduced into the bladder. The technique of distending the bladder was similar to that described by Helmstein (1972). The bladder was distended to a pressure equal to the patients' systolic blood pressure for 2 hours in 10 patients, 3 hours in 13 patients and only 1 hour, because of technical problems, in 2 patients.

Results

The cystoscopic findings were constant in showing small-capacity bladders which bled on filling, and later, shallow linear ulcers appeared in the vault. Biopsies taken from these areas showed chronic non-specific inflammation. Bladder capacity at initial cystometry varied from 55 to 300 ml (mean—151 ml). At the end of prolonged distension the capacity varied from 140 to 880 ml (mean—450 ml), and at cystometry 3-6 months postoperatively, the bladder capacities varied from 110 to 500 ml (mean—278 ml).

The patients' symptoms before and after prolonged bladder distension are shown in Tables I, II and III.

Preoperative cystometry revealed all the patients to have small-capacity hypersensitive bladders with no evidence of bladder instability, except in 1 patient who had detrusor instability which was reversed following prolonged bladder distension. No patient had a significant residual urine.

16 out of the 25 patients were symptom-free at the most recent follow-up, which varied from 3 months to 3½ years (mean—14 months). However, 5 of these 16 patients had had at least one previous prolonged bladder distension (Table IV). 6 patients were symptomatically improved and 1 of these patients had had a previous bladder distension. No symptomatic improvement occurred in 3 patients following bladder distension. 2 of the patients in the "improved" group and 1 patient in the "no change" group had initially been symptom-free for short periods (between 2 and 5 weeks), following prolonged bladder distension. The bladders of 2 patients were ruptured during prolonged bladder distension. These patients were treated by urethral catheter drainage of the bladder for 10 days, the catheter being removed after a normal cystogram. It was not necessary to drain the extravesical space. Both patients have done well postoperatively and remain symptom-free (1 year and 20 months).

Discussion

Our urodynamic studies have shown these patients to have small-capacity hypersensitive bladders. In our patients the capacity was limited by pain rather than by being contracted and non-distensible; as can be seen by comparing the bladder capacities of the patients at cystometry and then at the end of prolonged bladder distension. The pain produced on cystometry was identical to that of which they complained.

It follows that treatment should be aimed at a sensory denervation of the affected portion of the bladder. Pieri (1926) used a pre-sacral neurotomy in the management of the small contracted painful bladder, but with indifferent results. Nesbit in 1947 advocated anterolateral chordotomy for refractory interstitial cystitis with intractable pain and had good results in 4 out of 4 cases. Milner and Garlick (1957) and Mason, Haines and Leversee (1960) used selective sacral neurotomy of the third sacral root and claimed excellent results with relief of pain and some increase in capacity. The earliest description of local sensory denervation for interstitial cystitis is that by Learmonth (1931). He described a technique of denervation by cutting the pre-sacral nerve and branches of the hypogastric plexus around the terminal part of the ureter, having success in 3 out of 4 patients with interstitial cystitis, by relieving the pain but not improving the capacity.

More recently, Turner Warwick and Ashken (1967) described a new method of denervating the bladder by the technique of cysto-cystoplasty, in which the bladder is transected above the ureteric orifices and then re-sutured. Later, Worth and Turner Warwick (1973) described the lesser procedure of cystolysis as a means of denervating the bladder in the treatment of patients with interstitial cystitis. They concluded that cystolysis was an effective method of alleviating the bladder pain of patients (10 out of 10) with interstitial cystitis.

Prolonged bladder distension at a pressure equal to systolic blood pressure produces ischaemia and metabolic acidosis in the bladder wall of rabbits (Dunn, 1976) and some changes in submucosal nerve endings (Gosling, Dixon and Dunn, 1977). It would seem possible that ischaemic and/or mechanical damage to the submucosal afferent nerve plexuses or stretch receptors might be responsible for the loss of bladder pain and increase in bladder capacity following prolonged bladder distension.

Denervation would not be indicated in a patient whose bladder had undergone secondary contracture to a point at which it could not be distended, and in these patients, colo- or caecocystoplasty should be considered. Turner Warwick and Ashken (1967) treated 16 patients with interstitial cystitis by caecocystoplasty and all lost their pain.

It is important to recognise that carcinoma of the bladder may present with the same symptoms and similar cystoscopic appearances. It is therefore vital to biopsy the affected areas in every case to exclude multiple submucosal carcinoma. Smith and Badenoch (1965) reported a series of 12 patients with carcinoma of the bladder simulating chronic cystitis of whom 3 had been considered to have, and may well have had, interstitial cystitis for a number of years.

Conclusions

Prolonged distension of the bladder would seem to be a useful technique in the management of patients with interstitial cystitis. It is a relatively simple procedure and complications are few. The bladders of 2 patients were ruptured during distension (both these patients remain symptom-free) and 1 patient had a backache at the site of the epidural for 4 weeks postoperatively. The patient need only be in hospital for 2 days.

Summary

25 patients with interstitial cystitis were treated by prolonged bladder distension.

16 patients are symptom-free, but 5 of these have had 1 or more previous prolonged bladder distensions. 6 patients are improved, whilst 3 remain symptomatically unchanged. Prolonged bladder distension can be repeated successfully when symptoms return.

These results suggest that prolonged bladder distension has a place in the treatment of interstitial cystitis.

We are grateful to Miss Penelope Fursdon, Miss Wendy Hills and Mrs Pat Lewis for their technical assistance with the cystometry. We would like to thank our anaesthetist colleagues for providing epidural anaesthesia. We thank Miss Sarah Hunt for typing the manuscript.

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The Authors

M. Dunn, ChM, FRCS, Senior Urological Surgical Registrar, Bristol Royal Infirmary.

P. D. Ramsden, FRCS, Research Fellow, United Oxford Hospitals (now Senior Urological Registrar, Newcastle General Hospital, Newcastle upon Tyne).

J. B. M. Roberts, ChM, FRCS, Consultant Urological Surgeon, Bristol Royal Infirmary.

Joe C. Smith, MS, FRCS, Consultant Urological Surgeon, United Oxford Hospitals.

P. J. B. Smith, ChM, FRCS, Consultant Urological Surgeon, St Martin's Hospital, Bath, Avon.

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Abacterial Cystitis

P. T. DOYLE, G. F. ABERCROMBIE, J. D. JENKINS, C. J. SMART and J. VINNICOMBE
From the Departments of Urology, Portsmouth and Southampton

Over 30 years ago Moore (1940) described a condition which he called Abacterial Cystitis and there have been several other reports of this condition since (Coutts and Vargas-Zalazar, 1946; Czekalowski and Horne, 1951; Moore, Parker and Charlton Edwards, 1971). The patients had an acute cystitis, their urine contained pus and red blood cells and their intravenous urograms showed appearances similar to those seen in genito-urinary tuberculosis. No bacteria, however, were isolated from the urine. Over a 10-year period in the Portsmouth and Southampton Districts approximately 80 patients with acute cystitis and an initially sterile urine have presented. Most of these have proved to be genito-urinary tuberculosis, but among them have been the 5 cases we wish to present.

Patients and Results

All 5 were male patients whose ages ranged from 18 to 31. There were no common features in their employment. 2 were married and 3 single. They were referred because of the sudden onset of severe urgency and frequency of micturition, with terminal haematuria. 2 patients had a history or urethral discharge which had occurred on and off for a period of some years. 1 of them attended the Portsmouth Special Clinic but no organism was cultured from the discharge.

When first seen, all of these patients were micturating every 15 to 30 minutes, day and night. They had noticed terminal haematuria, which was heavy in the youngest patient and had noticed that their urine was cloudy but not offensive. The youngest patient had also noticed bilateral loin pain during micturition.

There was no history of any serious disease in any patient. 4 of them had received antibacterial treatment, but sulphonamides, ampicillin, cephalosporins, nitrofurantoin and nalidixic acid had produced no improvement and the pyuria persisted.

Most of the patients looked ill; 1 was admitted directly from Out-patients, a second shortly afterwards when his symptoms deteriorated, and a third as an emergency with increasing haematuria. All were apyrexial. 2 had suprapubic tenderness, and 2 had a tender prostate gland. 1 of the latter had a urethral discharge. The youngest patient was hypertensive, with a blood pressure of 150/115 mm Hg.

Repeated mid-stream specimens of urine showed pus and red blood cells, but there was no growth on culture, and repeated cultures for acid-fast bacilli were also negative. Haemoglobin estimations were all within normal limits and white cell counts varied from 6,000 to 13,000 per mm^3, with a normal differential count. In the most severe case the sedimentation rate was 13 mm per hour. The serum creatinine and urea estimations were normal and there were no other abnormal biochemical findings.

The intravenous urogram showed immediate renal function, with normal upper urinary tracts in 2 cases and bilateral clubbed calyces and dilated ureters in 3 cases (Fig. 1). The bladder outline in all the patients was small and irregular (Fig. 2). At cystoscopy the bladder capacity was much reduced and the mucosa intensely congested. The appearances were compatible with a diagnosis

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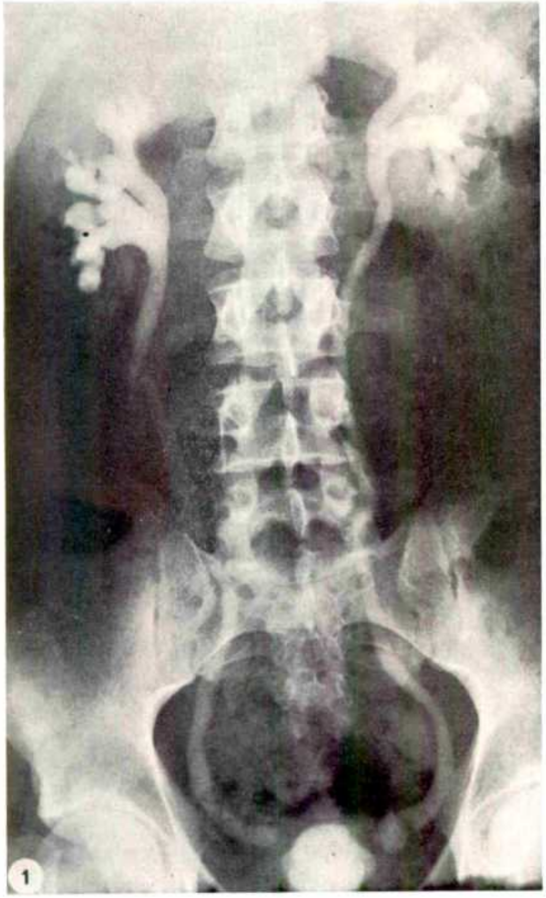
of vesical tuberculosis. Bimanual examination was normal with the prostate being reported normal in all cases. Biopsy of the bladder wall showed infiltration by acute and chronic inflammatory cells, including polymorphonuclear leucocytes, histiocytes and occasional lymphocytes, eosinophils and macrophages. In 1 case these changes were present in both bladder and prostatic biopsies.

The 2 early cases seen in Portsmouth were not treated at first, as tuberculosis seemed the likely diagnosis, and only after a long series of urine tests proved negative was any other diagnosis suspected. The symptoms in 1 of these patients settled spontaneously, but in the other patient the symptoms persisted unchanged for 4 months. "Abacterial cystitis" was then suspected and treatment with tetracycline was instituted. His symptoms immediately improved.

Other patients in the series were treated with tetracycline at a much earlier stage. A standard dosage of 250 mg 4 times daily proved quite sufficient. The blood and pus gradually disappeared from the urine and, in 2 patients, a follow-up intravenous urogram has shown much improved appearances. 3 patients have had a follow-up cystoscopy, one 3 months after treatment when normal appearances were reported, a second after 8 months because of a failing stream. There was



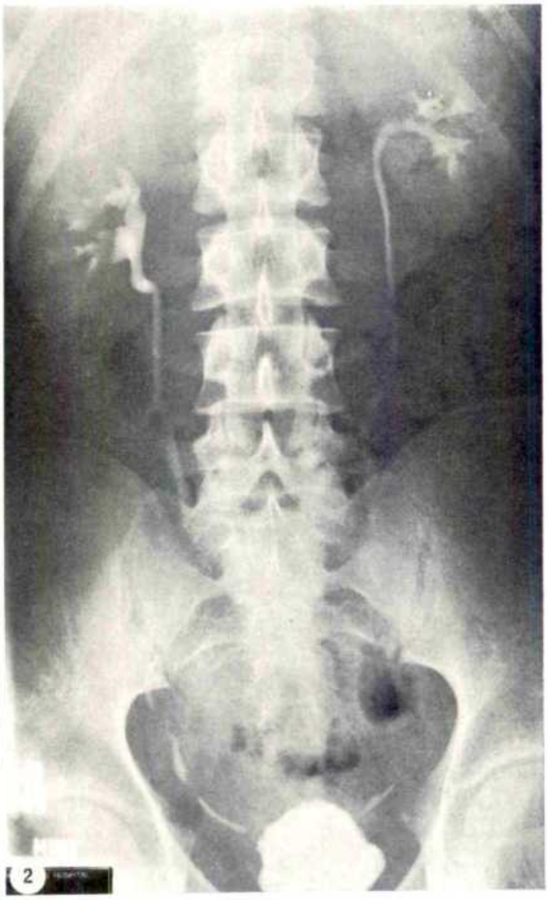


Fig. 1. Intravenous urogram showing typical appearances of small contracted bladder, dilated ureters and clubbed calices.

Fig. 2. Intravenous urogram showing irregular contracted bladder with normal upper urinary tracts.

a short bulbar stricture but the bladder was normal and the stricture settled after out-patient dilatation. A third case had a cystoscopy because of a recurrence of urethral discharge but the bladder appeared quite normal, as did the prostate.

The subsequent progress for each patient has been relatively uncomplicated. 1 had perineal aching and pain after intercourse, with occasional urgency of micturition. He has attended the Eye Department with idiopathic retinal haemorrhages, and a diagnosis of Reiter's disease was considered; however, his symptoms settled and no positive diagnosis was established. The most recent case, who was treated less than a year ago, is symptom free at present. His raised blood pressure on admission had settled at the time of his follow-up cystoscopy 3 months later.

Discussion

This condition seems to be a disease of young male patients. Donovan (1946) in his cases described an associated sterile urethral discharge. Goldstein (1947) reported severe cystitis associated with Reiter's Syndrome. Cultures of the urine in previous reports have never reliably established a cause although Coutts and Vargas-Zalazar (1946) found a spirilla in 5 cases and Czekalowski and Horne (1951) a spirochaete. The bladder seems to be principally affected. The 3 cases reported by Moore *et al.* (1971) all had normal upper urinary tracts, 1 patient was hypertensive. Hanky and Stept (1950) mentioned the value of tetracycline in this condition, and Moore *et al.* (1971) found organic arsenicals useful.

The cause of the condition has yet to be established. Although it has been called "Abacterial cystitis" the evidence would suggest that it is an infective condition, in that there is pus and blood in the urine, the bladder mucosa is inflamed, and the symptoms respond to tetracycline. The response to tetracycline makes a viral aetiology unlikely, but the pathogen might be a mycoplasma or chlamydia which is sensitive to tetracycline but not to other commonly used antibacterials. Mycoplasma are known to cause cystitis (Berg, Weinberger and Dienes, 1957). These organisms were not sought either in urine or from urethral discharge in any of our patients. If the pathogen was a bacteria, however, it is possible that it was not detected by the standard culture methods used. Our patients' mid-stream urines were cultured on MacConkey agar at the time they presented and it has been recognised since then that this medium does not reliably support the growth of *Staphylococcus albus*, one type of which, the micrococcus, is now known to be a cause of cystitis (Maskell, 1974). Furthermore, there are organisms known to be fastidious in various ways; they may be slow growing and require a longer incubation time than is usually used, or they may be micro-aerophilic or even anaerobic. Since this problem was discussed with a bacteriologist, our laboratory has recorded 3 cases in which a mid-stream urine sent in by a general practitioner from a young male with acute urinary symptoms showed pyuria and haematuria, but again no organisms on culture by routine techniques. Cultures were repeated using other media and longer incubation, a micrococcus was isolated from one, a strain of *Acinetobacter lwoffii* from a second, and a coliform from a third. With hindsight, therefore, it is impossible to say that there were no bacteria in these patients' urines.

The diagnosis of "Abacterial cystitis" should not therefore be made until careful bacteriological investigations have been undertaken. In this way, the causative organism or organisms might be established. This condition has a close similarity to genito-urinary tuberculosis and should be remembered in any young male patient with a sterile pyuria in whom acid-fast bacilli cannot be cultured.

Summary

5 young male patients with all the symptoms and signs of genito-urinary tuberculosis but in whom no organism could be cultured from the urine are described.

4 of them rapidly responded to a course of tetracycline.

Various organisms are suggested as a cause of this condition, and careful bacteriological investigation in the future might discover the cause.

I should like to thank the Surgeons of the Portsmouth and Southampton Districts for allowing me to publish their cases, and Dr R. Maskell of the Bacteriological Department, Saint Mary's Hospital, Portsmouth, for her helpful advice.

I should also like to thank Mr D. MacLean, Medical Photographer, Portsmouth District Hospitals, for his help in the preparation of the illustrations.

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The Authors

P. T. Doyle, FRCS, Senior Registrar, Department of Urology, St. Mary's General Hospital, Portsmouth.
G. F. Abercrombie, FRCS, Consultant Urological Surgeon, Portsmouth and S.E. Hants. Health District.
J. D. Jenkins, MChir, FRCS, Consultant Urological Surgeon, Southampton University Hospitals.
C. J. Smart, FRCS, Consultant Urologist, Southampton and S.W. Hants. Health District.
J. Vinnicombe, MChir, FRCS, Consultant Urological Surgeon, Portsmouth Hospitals Group.

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Psychiatric Aspects of Recurrent Cystitis in Women

D. L. P. REES and N. FARHOUMAND
St Peter's Hospitals, and St Bartholomew's Hospital, London

It has long been recognised by urologists that a number of women presenting with recurrent cystitis (including lower urinary tract infection, urethral syndrome and frequency/dysuria syndrome) suffer from psychiatric symptoms. Hitherto it has not been established how often this is a clinically significant problem, nor whether psychiatric manifestations, when they occur in these patients, are a contributory factor or a consequence of the physical condition. A relationship between bladder function and certain psychological factors (*e.g.* emotional changes and stressful experiences) has been recognised since the original reports of Mosso and Pellicani (1882), based on cystometric experiments, confirmed and extended by the work of Straub, Ripley and Wolf (1949). More recently the observations of Jeffcoate and Francis (1966), Frewen (1972) and Hafner, Stanton and Guy (1977) have added to our understanding of psychogenic factors in patients with urge incontinence.

There have been significant advances in recent years in techniques for accurately assessing psychological and psychiatric as well as urological factors in patients. This study has used these techniques to evaluate the importance of psychological and psychiatric manifestations in women with recurrent cystitis.

Patients

During a two-year period (1974-1976) 242 women with recurrent attacks of dysuria and increased frequency of micturition were referred to the Urinary Infection Clinic at the Institute of Urology. 15 women were excluded from the study because of a major abnormality on i.v. urography, and 12 were unable or unwilling to be admitted to hospital for investigation. There remain 207 patients who have been fully assessed urologically. Of these, 50 successive unselected admissions also underwent detailed psychological and psychiatric assessments, and are the subject of this study. The age range was 16 to 62 years with a mean of 34·5 years.

Methods

All patients were subjected to a standard investigation routine. In addition to general, urological, gynaecological and sexual histories, a full psychiatric interview was undertaken by one of us (N. F.). This focused on past and current psychiatric symptoms and their relationship to the onset of micturition symptoms.

Three psychometric tests were used.

1. *The Eysenck Personality Questionnaire—E.P.Q.* (Eysenck and Eysenck, 1975)

This measures Extroversion/Introversion (E.); Neuroticism or emotionality (N.); Psychoticism or toughmindedness (P.); and also provides a Lie scale (L.). There is evidence that the components of personality structure (particularly N.) as measured in this test have an hereditary basis (Shields, 1962; Eysenck, 1967).

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

2. *The Morbid Anxiety Inventory—M.A.I.* (Salkind, 1969)

This measures the degree of anxiety on a scale distinguishing between normal and clinical anxiety. Three sets of questions in this inventory relate to micturition, sex and sleep dysfunction, therefore had to be eliminated and a correction factor applied to remove this potential source of error.

3. *The Middlesex Hospital Questionnaire—M.H.Q.* (Crown and Crisp, 1966)

This provides six subscales: Free floating anxiety (F.F.A.); Phobic anxiety (PHO.); Obsessionality (OBS.); Somatic concomitants of anxiety (SOM.); Depression (DEP.) and Hysterical traits (HYS.).

The HYS. subscale has also been shown to include an extroversion component (Cockett, 1969). Control data for this test have been taken from the studies of Crisp and Priest (1971) and Howell, Crown and Howell (1973).

These three questionnaires were selected for use as they show high validity and reliability, give a broad psychometric profile and are standardised for the British population. Data relating to the E.P.Q. and M.H.Q. provide age and sex matched controls (normal and psychiatric) for comparison with the patients in this study. Care was taken to ensure that all patients completed the questionnaires under similar conditions and that none was influenced by contact with other patients who had already been assessed.

Urological Evaluation

In addition to routine physical examination all patients had repeated urine and introital bacteriology, routine haematology and serum biochemistry, chest X-ray and i.v. urography. The

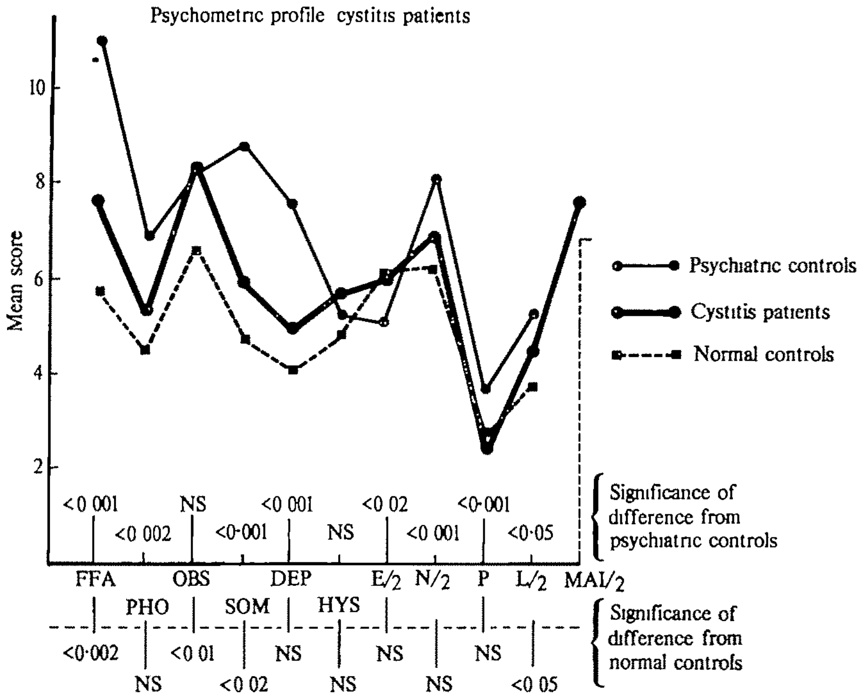

Fig. 1. Psychometric profiles: cystitis patients. NS = No significant difference. Subscores: F.F.A. = Free floating anxiety; PHO. = Phobic anxiety; OBS. = Obsessionality; SOM. = Somatic concomitants of anxiety; DEP. = Depression; HYS. = Hysterical traits; E. = Extraversion; N. = Neuroticism; P. = Psychoticism; L. = Lie scale; M.A.I. = Morbid Anxiety Inventory.

urodynamic assessment included residual urine measurement by catheterisation prior to recording the urethral pressure profile performed by the method of Brown and Wickham (1969) as modified by Harrison and Constable (1970). Cystometry was performed with the patient seated on a modified commode, with a filling rate of 150 ml/min routinely used. Values for maximum voiding pressure and peak urine flow rate were obtained. Urethral calibration was performed before cystoscopy and pelvic examination under general anaesthesia.

Numerous clinical subdivisions of patients were established. The threshold values (*e.g.* flow rate of 11 ml/sec or less) used for defining subgroups on urodynamic grounds, have been chosen as being 1 standard deviation from the mean of a large number of urodynamic estimations (Rees *et al.*, 1976). The Student *t*-test was used to establish the significance of differences of mean scores between the cystitis patients and the controls.

(a) *Bladder instability* (uninhibited systolic detrusor contractions on filling cystometry), was demonstrated in 7 patients (14%). A further 8 patients had end filling pressures of 15 cm H_2O or more without uninhibited detrusor contractions.

(b) *Inhibited micturition* is defined by one of us (D. L. P. R.) as an absence of anatomical outlet obstruction (urethral calibre of 20 FG or more) with a peak flow of 11 ml/sec or less produced by an adequate detrusor pressure (20 cm H_2O or more). Added to this group are those who also had no evidence of anatomical obstruction but were unable to void during the test. 11 patients (22%) were found to fall into this category of inhibited micturition.

(c) *Bladder outlet obstruction* was considered to exist in patients with a urethral calibre of 19 FG or less, who could produce peak flow rates of no better than 11 ml/sec despite a reasonable maximum voiding pressure (20 cm H_2O or more). Only 3 patients (6%) fulfilled this definition. This small percentage compares well with that found by Rees *et al.* (1976).

(d) *A low detrusor voiding pressure* was found in 10 patients (20%), in whom the maximum voiding pressure was 19 cm H_2O or less.

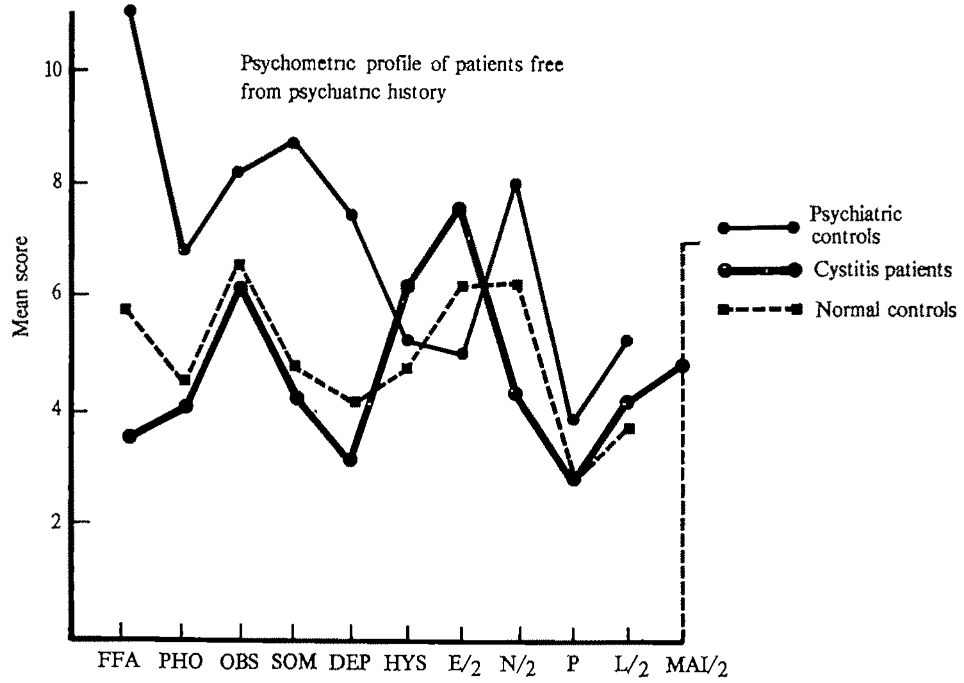

Fig. 2. Psychometric profile: patients free from psychiatric history. (See Fig. 1 for key.)

Table I

			Middlesex Hospital Questionnaire						Eysenck personality questionnaire				
			F.F.A.	PHO.	OBS.	SOM.	DEP.	HYS.	E	N	P	L	Corrected M.A.I.
Age and sex matched controls	Normal (*n* = 604–3262)	Mean score	5·95	4·50	6·75	4·75	4·15	4·80	12·60	12·74	2·63	7·73	14·00
		S.D.	±3.6	±2·9	±3·5	±3·0	±3·0	±3·05	±4·83	±5·20	±2·36	±4·18	or less
	Psychiatric (*n* = 173–404)	Mean score	11·0	6·8	8·2	8·9	7·6	5·2	10·02	16·22	3·67	10·59	
		S.D.	±3·5	±3·9	±3·8	±3·9	±3·9	±3·5	±5·05	±4·59	±2·95	±4·83	
Patients with recurrent cystitis	(*n* = 50)	Mean score	7·70	5·22	8·26	5·92	4·86	5·66	11·96	13·84	2·50	9·04	15·42
		S.D.	±3·60	±3·01	±3·27	±3·21	±2·89	±2·95	±5·54	±4·65	±2·22	±4·49	±6·94
Bladder instability	(*n* = 7)	Mean score	9·00	4·14	6·43	7·86	4·86	5·14	11·29	13·00	5·00	9·29	15·43
		S.D.	±4·00	±2·48	±3·6	±3·34	±4·95	±4·38	±6·65	±4·08	±3·37	±4·79	±7·37
High end filling pressure on cystometry	(*n* = 15)	Mean score	8·07	4·67	7·93	6·80	5·13	5·27	9·87	14·73	3·20	8·33	14·8
		S.D.	±4·20	±2·53	±3·90	±3·14	±3·89	±3·69	±6·27	±4·59	±2·96	±4·40	±7·34
Inhibited micturition	(*n* = 11)	Mean score	8·82	4·82	8·55	6·36	5·73	5·91	10·55	13·82	2·09	7·91	16·82
		S.D.	±4·17	±3·46	±3·27	±2·94	±3·72	±3·88	±4·95	±5·00	±1·87	±4·18	±7·61
Bladder outlet obstruction	(*n* = 3)	Mean score	8·33	4·00	8·67	7·00	6·00	4·67	16·00	17·67	3·33	10·67	17·33
		S.D.	±3·06	±1·00	±3·21	±3·61	±2·00	±0·58	±1·00	±3·51	±1·15	±4·93	±3·21
Low detrusor voiding pressure	(*n* = 10)	Mean score	6·70	5·70	8·00	6·70	5·80	7·30	12·50	11·90	2·30	9·10	13·80
		S.D.	±3·56	±3·95	±2·40	±4·14	±3·52	±4·62	±5·68	±4·91	±1·64	±5·28	±6·75
Bacteriuria	(*n* = 14)	Mean score	7·00	5·93	8·50	5·86	5·50	5·50	10·50	13·50	3·07	10·57	15·21
		S.D.	±3·55	±3·29	±4·42	±2·63	±2·95	±2·21	±6·55	±5·16	±2·64	±4·65	±7·77
Dyspareunia	(*n* = 22)	Mean score	8·91	5·55	8·59	5·91	4·64	6·27	12·95	14·77	2·68	8·59	18·00
		S.D.	±3·08	±3·02	±3·08	±3·01	±2·42	±2·39	±4·73	±4·16	±1·96	±3·98	±6·38

(e) *Bacteriuria* was established by finding 10^5 organisms/ml in any clean catch or cystoscopy specimen of urine in 14 patients (28 %).

(f) *Dyspareunia* was reported by 22 patients, forming a futher subgroup.

(g) *Other groups* also analysed included abacteriurics, patients with high urethral resistance (maximum voiding pressure/peak flow rate[2]) and those with a high urethral pressure profile. Patients complaining of urgency, urge incontinence or nocturia in addition to their presenting symptoms of recurrent dysuria and increased frequency, formed 3 further subgroups.

Findings

1. *Psychometric Questionnaires* (Table I)

Patients with recurrent cystitis as a whole

The study group showed interesting differences from the normal controls and from psychoneurotic psychiatric out-patients. They demonstrated more free floating anxiety (F.F.A.), obsessionality (OBS.) and somatisation (SOM.) than normals at statistically significant levels (Fig. 1). On the other hand they were not significantly different from normals on the subscales for phobic anxiety (PHO.), depression (DEP.), neuroticism (N.) and psychoticism (P.). Cystitis patients had the same scores as psychiatric controls on the subscales OBS. and HYS, (hysterical traits).

The M.A.I., corrected as described above, confirmed the high prevalence of anxiety (Table II).

(a) *Bladder Instability.* These patients had even higher subscores for F.F.A. and SOM., but were normal for other subscales except P. in which the mean score of 5·0 ± 3·37 was nearly twice that of normal but just failed to reach statistical significance because of small numbers. A similar

Table II

Salkind's Morbid Anxiety Inventory (corrected)

	Score	Cystitis patients
Normal	(0-14)	22
Clinical anxiety	(15-25)	23
Severe clinical anxiety	(26+)	5
Total		50

Mean score 15·42 ± 6·94.

Table III

Past History of Psychiatric Symptoms

	Antedating cystitis	Secondary to cystitis	Not relatable to cystitis	Total
Anxiety alone	5	4	1	10
Depression alone	2	5	4	11
Anxiety and depression	7	1	1	9
Total	14	10	6	30

psychometric profile was obtained for patients with a high end-filling pressure on cystometry but with a more normal P. score.

(b) *Inhibited Micturition.* This group also had significantly higher scores for F.F.A. than normal controls. OBS. was also higher than normal but not reaching statistical significance. For F.F.A. and OBS. the figures are similar to those of the psychiatric control group, but approximated to normality in the other subscales.

(c) *Bladder Outlet Obstruction.* In addition to a high score for F.F.A. this small group had an OBS. score well in excess of the psychiatric controls. The most interesting feature of this group, however, was very significantly high E. and N. scores in the E.P.Q. which distinguishes them from all other patients in the study. (Significance of difference from normal controls: for E., $P<0{\cdot}001$; for N., $P<0{\cdot}02$.)

(d) *Low Detrusor Voiding Pressure.* These patients showed significantly less anxiety than the other subgroups. Scores for OBS. and HYS., however, were similar to those of psychiatric controls.

(e) *Bacteriuria.* There was no difference between bacteriuric patients and the study group as a whole. Due to smaller numbers the elevated F.F.A., OBS. and SOM. scores did not reach a statistically significant difference from normals.

(f) *Dyspareunia.* As well as the now familiar high scores for F.F.A. and OBS., women complaining of difficulty and pain with intercourse also had significantly elevated HYS. and N. scores ($P<0{\cdot}01$).

(g) *Other Groups Analysed.* Patients with a high calculated urethral resistance and a high urethral pressure profile did not differ from the study group as a whole in any of the subscores. Those patients with urge incontinence had significantly higher HYS. scores. Other symptoms such as nocturia and urgency without incontinence were not associated with any characteristic changes in the psychometric profiles.

The subscores were also analysed against age. The significant findings here were that all scores on the M.H.Q. tended to increase with age but only DEP. and HYS. significantly so. Young patients with bladder instability had a particularly high SOM. score ($7{\cdot}75 \pm 1{\cdot}83$) compared with age and sex matched undergraduate controls ($3{\cdot}8 \pm 2{\cdot}7$, $P<0{\cdot}001$).

In summary: these psychometric tests revealed significant differences (marked obsessionality and clinical anxiety in particular) between women with cystitis and age and sex matched normal controls. Hysterical traits were more common in patients with urge incontinence or dyspareunia, and with increasing age. High N. (neuroticism) scores were found in those with bladder outlet obstruction and dyspareunia.

2. *Psychiatric Interview*

Assessment by interview is subjective; thus care has to be taken to keep to a uniform and standardised format. 2 patients were difficult to assess and are not included in this part of the analysis. One was a pathological liar with a severe personality disorder; the other was totally deaf.

Table IV

Psychiatric State on Admission

Anxiety alone	15
Depression alone	2
Anxiety and depression	12
Total	29

Table V

Follow-up Analysis

	No.	%
Cured	39	86·7
Improved	4	8·9
Same	2	4·4
No follow-up	5	

Mean follow-up 21·4 months ± 4·3.
Cured = asymptomatic and abacteriuric.
Improved = minimal symptoms insufficient to lead patients to seek further medical advice.

14 patients (30% of 48) had a history of anxiety and/or depression antedating the onset of micturition symptoms. In this group these psychiatric manifestations cannot be regarded as a reaction to or a consequence of the urological disorder; whereas in 10 patients (24%) they can (Table III). 29 patients (60%) were considered clinically anxious, depressed or both at the time of interview (Table IV).

Only 12 patients (25%) were found to have been free from psychiatric symptoms at all times. The psychometric profile of this group was very similar to that of normal controls except for a high mean score for extroversion (Fig. 2). Perhaps an extrovert personality protects patients with recurrent cystitis against psychiatric disturbance. The scores were significantly different from the study group as a whole for F.F.A. ($P<0{\cdot}001$), DEP. ($P<0{\cdot}02$), N. ($P<0{\cdot}001$) and mean M.A.I. ($P<0{\cdot}001$).

Discussion

The most striking feature of this study is the high prevalence of anxiety. This applies to all subgroups with the exception of patients with low detrusor voiding pressure suggesting a direct link between anxiety and voiding pressure. Patients with dyspareunia were the most anxious and this might be responsible for increased perineal muscle tone amongst other factors.

It could be suggested that the majority of patients who are admitted to hospital are anxious to a degree and this is probably true. However, the M.A.I. gives a measure of morbid anxiety as opposed to normal anxiety.

This study has revealed a high incidence of psychiatric symptoms in women with recurrent cystitis; 60% compared with 6% in the general population (Rees, 1977). ($\chi^2=32{\cdot}97$; $P<0{\cdot}001$). The second National Morbidity Survey carried out in 1970–71 by the Office of Population Censuses and Surveys revealed that 96 females per 1,000 per year attended general practice with a diagnosis of anxiety and/or depressive neurosis (Secretary of State for Social Services, 1975). That there is a psychiatric predisposition to recurrent cystitis is suggested by the much higher than expected incidence of psychiatric symptoms (30%) antedating the onset of micturition symptoms ($\chi^1=5{\cdot}76$, $P<0{\cdot}025$), and confirmed by raised mean scores in the E.P.Q. (particularly the N. subscore), more marked in some clinical subgroups than others (*e.g.* outlet obstruction and dyspareunia).

In this study there has been high correlation between the 3 psychometric questionnaires used, where subscores measured the same components (*e.g.* F.F.A. and PHO. versus M.A.I., and HYS. versus E.); also between the questionnaires and the clinical psychiatric assessment, adding to the validity of the observations.

It should not be concluded from the results of this study that the majority of women presenting with recurrent cystitis should seek psychiatric rather than urological referral. 6 to 7% of these patients have urological abnormalities requiring major surgery (Rees *et al.*, 1976). A much larger percentage have gynaecological, neurological, bacteriological and lesser urological abnormalities of significance. The recognition of psychological and psychiatric factors in women with recurrent cystitis (a group of conditions of multifactorial aetiology), will enable a more balanced, sympathetic and fruitful approach to these patients to be made. That a multifactorial concept is therapeutically advantageous is suggested by the follow-up analysis of the study group (Table V). These percentages are similar to the overall results of the Urinary Infection Clinic as a whole.

Summary

Using both psychometric questionnaires and psychiatric interview it has been shown that women with recurrent cystitis have significantly more psychiatric symptoms (particularly those of anxiety) than the population as a whole.

By comparison with the expected prevalence, the study group shows a 3-fold increase in psychiatric symptoms antedating micturition symptoms, and a 10-fold increase in psychiatric symptoms overall.

Significant differences in psychometric profiles have been demonstrated between different clinical subgroups of patients (*e.g.* bladder instability, outlet obstruction and dyspareunia).

A multifactorial approach (including an awareness of psychiatric factors) to patients complaining of recurrent cystitis can produce a treatment failure rate as low as 4·4%.

We wish to thank Professor W. L. L. Rees for his constructive and helpful guidance in planning and carrying out this study, Miss Freda Wadsworth for preparing the illustrations, and Miss Anthea Minchom for preparing the typescript.

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The Authors

D. L. P. Rees, FRCS, Senior Registrar, St Peter's Hospitals.
N. Farhoumand, MRCPsych, DPM, Senior Registrar, St Bartholomew's Hospital.

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The Effect of N-Acetyl Cysteine on Cyclophosphamide Cystitis

D. A. TOLLEY
Department of Urology, King's College Hospital, Denmark Hill, London SE5

Cyclophosphamide is perhaps the most commonly used alkylating agent, having been in clinical use since 1960. Urological complications due to its administration are well documented following the initial reports of transient cystitis by Coggins, Randin and Eisman (1959). As well as haemorrhagic cystitis which may be fatal (Spechter *et al.*, 1965), widespread interstitial fibrosis may follow long-term administration (Johnson and Meadows, 1961; Marsh *et al.*, 1971). Damage to the urinary tract caused by cyclophosphamide is due to direct contact between urothelium and toxic metabolites of cyclophosphamide excreted in the urine (Phillips *et al.*, 1961). N-acetyl cysteine, a mucolytic agent used in clinical practice, neutralises the toxicity of alkylating agents (Brandt and Griffin, 1951).

The potential use of N-acetyl cysteine as a means of preventing cyclophosphamide cystitis has already been described (Tolley and Castro, 1975) and this paper presents the results of further experimental work.

Methods

Adult Wistar female rats were anaesthetised with ether. Injections of cyclophosphamide and other drugs were made intraperitoneally or intravenously into a tail vein. Rats were killed with an overdose of pentobarbitone sodium (Nembutal) and histological sections of the bladder were prepared (Tolley and Castro, 1975).

The cytotoxicity experiments were conducted using Wistar male rats injected with 1·0 ml of an ascitic form of the Walker 256 tumour containing approximately 10^6 cells into a hind limb. Rats were given various doses of cyclophosphamide or cyclophosphamide and N-acetyl cysteine (100 mg/kg) in a phosphate buffer pH 7·4 (Fig.), and killed 1 week later. The weight of residual tumour was used as an index of the cytotoxic efficacy of the chemotherapeutic agents used.

Histological assessment was made without prior knowledge of treatment and the changes graded according to the following criteria:

1. Normal histology—Normal epithelium, no inflammatory cell infiltration.
2. Mild changes—Epithelial flattening and submucosal oedema.
3. Severe changes—Mucosal erosion, inflammatory cell infiltrate, fibrin deposition and haemorrhage.

Results

A total of 190 rats were treated with cyclophosphamide or with a combination of cyclophosphamide and another compound.

The Table shows the efficacy of various agents given in conjunction with cyclophosphamide for preventing cystitis. N-acetyl cysteine (100 mg/kg) when given intraperitoneally effectively reduced

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Table

To show the Effect of Various Agents on Cyclophosphamide Cystitis

Therapeutic agent and dose in mg/kg		Histological changes		
		Severe	Mild	None
Hydrocortisone	100	2	3	0
Hydrocortisone	50	4	1	0
Ethamsylate	100	3	1	0
Ethamsylate	50	5	0	0
Saline diuresis		4	1	0
N-acetyl cysteine	10	4	2	0
	25	1	4	0
	50	0	3	3
	75	1	2	3
	100	0	0	6
	150	0	1	5
	200	6	0	6

the degree of cyclophosphamide cystitis for up to 18 hours after injection. When cyclophosphamide was given 24 hours after an intraperitoneal injection of N-acetyl cysteine (100 mg/kg) only 60% of rats developed severe cystitis compared with all rats receiving cyclophosphamide only.

When cyclophosphamide (10 mg/kg) was given weekly to rats they all developed severe intramural fibrosis of the bladder after three months. However, if N-acetyl cysteine (10 mg/kg) was given concurrently, then the bladders were histologically normal. Rats which were treated with N-acetyl cysteine (10 mg/kg) weekly for 3 months, after receiving 120 mg/kg of cyclophosphamide in divided doses over 12 weeks, developed severe fibrosis, which was as marked as the appearances in rats which received no treatment for 3 months, after receiving identical doses of cyclophosphamide.

The effect of N-acetyl cysteine on cytotoxic efficacy of cyclophosphamide, as assessed by the Walker quantitative tumour inhibition and toxicity test, showed no difference in the LD50 for animals receiving cyclophosphamide alone or cyclophosphamide in combination with N-acetyl cysteine. There was insignificant impairment of tumour toxicity as determined by the percentage weight loss for tumour (Fig.). These results have been reported in detail elsewhere (Tolley, Cox and Castro, 1977).

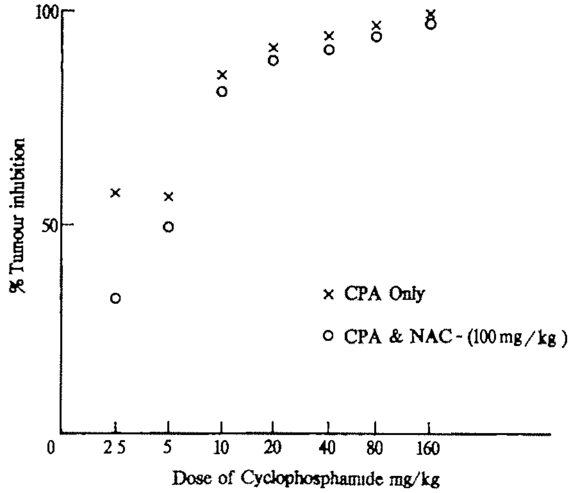
Discussion

The results indicate that cyclophosphamide induced cystitis may be prevented effectively by the administration of N-acetyl cysteine. In order to provide maximum protection N-acetyl cysteine should be given in a dose ratio of 1 : 1 (wt : wt) with cyclophosphamide and should be given within 2 hours of cyclophosphamide administration.

We have shown that provided N-acetyl cysteine is given throughout cyclophosphamide therapy, protection is continued for up to 3 months (the maximum duration of our experiment), but that N-acetyl cysteine, if given after a course of cyclophosphamide, does not speed resolution of the inflammatory changes, neither does it reverse fibrosis when it occurs.

We have previously provided indirect evidence to suggest that N-acetyl cysteine does not impair the cytotoxic efficacy of cyclophosphamide (Tolley and Castro, 1976) and the results of this work provide further direct evidence of this.

It would seem that N-acetyl cysteine is of value in protecting patients at risk of developing



cystitis and that it may be used without impairing the therapeutic efficiency of cyclophosphamide, provided that the dose ratio of N-acetyl cysteine to cyclophosphamide is not greater than 1. Its routine use in patients most at risk (children and those receiving high doses of intravenous cyclophosphamide) is recommended.

Summary

Further studies on the effect of various compounds of the rat bladder after treatment with cyclophosphamide are reported.

The results show that N-acetyl cysteine is a highly effective drug for the prevention of cyclophosphamide cystitis.

N-acetyl cysteine does not significantly impair the anti-tumour effect of cyclophosphamide.

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The Author

D. A. Tolley, FRCS, Senior Registrar.

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T1 Bladder Tumours

J. L. WILLIAMS, J. C. HAMMONDS and N. SAUNDERS
Department of Urology, Hallamshire Hospital, Sheffield

Although the prognosis of patients with a T1 bladder tumour is good, some 15% subsequently develop invasive tumours (Mills, 1964). We have reviewed the progress in our patients who presented with stage 1 tumours.

Patients

167 patients with a T1 bladder tumour were seen between 1962 and 1971. The age range was 33 to 84 with an average of 66 years. The male: female ratio in patients with single tumours was 3 : 1, and 6 : 4 in patients with multiple tumours.

Symptoms

88% of our patients presented with haematuria, the others having urinary tract infections or, rarely, retention of urine. 70% of the tumours were seen on the intravenous urogram as a filling defect in the bladder. 50% of the patients presented within 1 month, 81·5% within 6 months. There was a difference in the length of history in those patients with single (6 months) and multiple tumours (3.4 months). There is a similar difference when comparing those patients with invasion into the lamina propria (3·6 months) and those without invasion (5·2 months). The length of the history made no difference to the size of the tumour at the time of diagnosis. Those patients with well-differentiated tumours with a low pleomorphism and mitotic rate presented later (5·6 months) than those with moderate differentiation, pleomorphism and mitotic rate (3.6 months). Those patients with poor differentiation, a high pleomorphism and mitotic rate presented about 6 months, but the number of these patients is small.

T Category

The diagnosis was confirmed by a transurethral biopsy as part of the initial treatment in all patients. A T1 lesion was diagnosed on clinical assessment under anaesthesia and histologically, with the tumour being confined to the mucosa or showing invasion into the lamina propria only (P1). It is possible that some of the patients were understaged, but from their subsequent history this was thought to have occurred in only 2 who were found on the next transurethral resection to have invasive tumour.

Treatment

All these patients had their tumours treated by transurethral resection or cystoscopic diathermy. No patient had the bladder opened to remove the tumour. When transurethral resection was performed, the tissue was always sent for histological assessment. Radiotherapy was given to patients with high-grade tumours or those who subsequently developed an invasive tumour. Intravesical chemotherapy (thiotepa or Epodyl) was given to those patients with recurrent tumours.

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

Cystectomy was done for multiple tumours not controlled by other means and to patients with invasive tumours not responding to radiotherapy.

Pathology

All the tumours were transitional cell carcinoma; 1·8% had glandular metaplasia and 6·2% squamous metaplasia. The degree of differentiation was classified as being either well, (68·7%),

Table I

T1 Bladder Tumours 1977

	Invasion lamina propria %	Pleomorphism Low %	Pleomorphism Mod. %	Pleomorphism High %	Mitotic rate Low %	Mitotic rate Mod. %	Mitotic rate High %
Well differentiated	18	62	35	3	94·5	5·5	0
Moderately differentiated	49	20	60	20	55	29	16
Poorly differentiated	100	0	20	80	0	50	50

Table II

T1 Bladder Tumours 1977.
Total Survival at 3 years and 5 years ( )%

No. of patients	167
Survival	83·2 (71·8)
Tumour death	3·6 (4·2)
Other death	6·0 (7·8)
Lost	7·2 (16·2)
Persistent tumour	32·4 (26·6)

Table III

T1 Bladder Tumours 1977.
Survival at 3 years and 5 years ( )%

No. of patients:	Single 124	Multiple 41
Survival	83·8 (73·3)	83 (70)
Tumour death	3·2 (4·0)	5 (10)
Other death	4·0 (6·4)	7 (10)
Lost	9·0 (16·0)	5 (10)
Radiotherapy	4·0	7·3
Cystectomy	0·8	9·7
Chemotherapy	2·4	4·0

Table IV

T1 Bladder Tumours 1977.
Pleomorphism.
Survival at 3 years and 5 years ( )%

No. of patients:	Low 68	Moderate 59	High 17
Survival	86·8 (73·0)	81·4 (71·2)	76·4 (58·8)
Tumour death	0·0 (0·0)	8·4 (11·8)	11·7 (11·7)
Other death	4·4 (10·3)	6·8 (11·8)	5·8 (11·6)
Lost	8·8 (14·7)	3·4 (10·2)	5·8 (18·2)
Radiotherapy	0·0	8·4	18·2
Cystectomy	0·0	6·7	11·6
Chemotherapy	4·1	5·0	0·0

moderate (24·4%) or poor (6·8%). 47·2% of the tumours were of low pleomorphism, 40·9% moderate and 11·8% high. Mitotic activity was low in 74·8%, moderate in 16·1% and high in 9·1%.

In general there was similarity between the degree of differentiation of the tumour and the mitotic rate, but the degree of pleomorphism varied. 27·3% of the patients had invasion into the lamina propria (Table I).

Results

The total crude survival figures are given in Table II.

Single Tumours

50% of these patients were rendered tumour free by endoscopic means. 19·3% of them, however, did develop multiple tumours of the bladder at some time but they were equally divided amongst those patients having transurethral resection and those treated by cystodiathermy. 29·9% developed a single recurrence on one or more occasions. Few of these patients had radiotherapy or cystectomy.

Multiple Tumours (Table III)

There is little difference in the overall survival of these patients and those with single tumours, but only 30% were rendered tumour free by endoscopic treatment and 44% of them developed multiple recurrences. Single recurrences occurred in 14·8%. Many more had radiotherapy and cystectomy but this was related to the fact that whereas only 21% of the single tumours had invasion into the lamina propria, this was present in 43·9% with multiple tumours.

Cellular Characteristics and Differentiation

The overall survival for patients with tumours of well and moderate differentiation were similar but the incidence of radiotherapy and cystectomy rose and this is high in those patients with poorly differentiated tumours. A similar trend is seen for pleomorphism and mitotic activity. There is no statistical difference in the number of patients dying from their tumour when one compares the degree of differentiation and mitotic rate. The difference was significant ($P < 0.05$) in the number dying with a moderate or high pleomorphism compared with those with low pleomorphism (Table IV). It is significant that none of the patients with low pleomorphic tumours had a cystectomy or radiotherapy.

Table V

T1 Bladder Tumours 1977.
Invasion into Lamina Propria—Single Tumours

No. of patients:	Not invaded 97	Invaded 27
Survival	84·5 (75·3)	81·5 (66·7)
Tumour death	2·1 (3·1)	7·4 (7·4)
Other death	3·1 (3·1)	7·4 (11·1)
Lost	10·3 (16·5)	3·7 (14·8)
Radiotherapy	3·1	7 4
Cystectomy	0·0	3·7
Chemotherapy	2·1	0 0

Table VI

T1 Bladder Tumours 1977.
Invasion into Lamina Propria—Multiple Tumours. Survival at 3 years and 5 years ( )%

No. of patients:	Not invaded 23	Invaded 18
Survival	87·0 (74·0)	77·8 (66·7)
Tumour death	0·0 (0 0)	11·1 (22·2)
Other death	4·3 (8·7)	11·1 (11·1)
Lost	9·0 (18·2)	0·0 (0·0)
Radiotherapy	0·0	16·7
Cystectomy	0·0	16·7
Chemotherapy	0·0	16·7

Invasion into the Lamina Propria (Tables V and VI)

If one compares the number of patients dying from their tumour to the invasion of the lamina propria, significantly more died when there was lamina propria invasion ($P<0{\cdot}05$). This is particularly so with multiple tumours. All patients with multiple tumours without lamina propria invasion had their tumours controlled endoscopically; not one had a cystectomy or radiotherapy, and none died of their tumour. The results in patients with single tumours show that a few died of tumour, none had a cystectomy and few radiotherapy.

Radiotherapy

17 (10%) of these patients had a course of radiotherapy, the majority having a radical course (5,800 rads in 5 weeks) on the linear accelerator or cobalt unit.

8 had treatment following the first biopsy. They all had invasion into the lamina propria with a high or moderate mitotic rate and pleomorphism and poor or moderate differentiation. 25% of them died within 5 years of their tumour.

5 patients had radiotherapy for invasive tumours developing within 6 months to 5 years after the original diagnosis. It is possible that 2 of these were understaged initially. The mortality is high and of the 3 survivors, 2 have recurrent tumour.

4 patients had radiotherapy for invasive tumour developing 5 years after the original diagnosis; 3 died from tumour within one year, the fourth is still alive with tumour.

Invasive Tumours

13 patients developed invasive tumours. The length of time after the original diagnosis is given in Table VII. The number with single and multiple tumours was the same. These tumours presented quite suddenly and the prognosis was bad. The characteristics of the original tumour are given in Table VIII. In 62% there was invasion into the lamina propria; the mitotic rate was high or moderate in 84% and pleomorphism high or moderate in 92%. 58·9% of the tumours were moderately or poorly differentiated.

Table VII

T1 Bladder Tumours 1977.
Muscle Invasion (13).
Length of Time for Invasive Tumours to appear after Initial Diagnosis in 13 Patients

<6/12 months	1
6/12-1 year	1
1-2 years	2
2-3 years	1
3-4 years	2
4-5 years	3
5+ years	3

Table VIII

T1 Bladder Tumours 1977.
Muscle Invasion.
Cellular Characteristics in the Initial Tumour in Patients developing Invasive Tumours compared with the Total Series

		%		% in series	
No. of patients: 13				8	
Lamina propria invasion		62·0		29·9	
Pleomorphism	High	23·0	92·0	10·2	45·5
	Moderate	69·0		35·3	
	Low	8·0		40·7	
Mitotic rate	High	46·0	84·0	7·8	21·5
	Moderate	38·0		13·7	
	Low	16·0		64·1	
Differentiation	Well	46·1		68·7	
	Moderate	30·8	58·9	24·4	31·3
	Poor	23·1		6·9	

Cystectomy

8 patients had a cystectomy, 2 following radiotherapy. 2 of these patients died following the operation. 1 from pulmonary emboli and the other from dehiscence of the incision as a result of the radiotherapy.

The survival of the others is good.

Discussion

These results are in agreement with those published by Miller, Mitchell and Brown (1969) Pomerance (1972), Anderson (1973) and Pryor (1973) for non-invasive tumours (Table IX). It is difficult to compare the results for invasion into the lamina propria because of differences in classification, but Pryor (1973) gives a figure of 64% survival at 3 years and Pomerance (1972) 40% at 3 years and 27% at 5 years in those patients treated by cystectomy. Many of these patients had had radiotherapy before the cystectomy. It is generally recognised that poor differentiation and a high mitotic rate are adverse factors, but Pomerance (1972) could find no difference in the prognosis with pleomorphism. Our results show that the degree of pleomorphism varied much more than the mitotic rate with the differentiation of the tumour and there were significantly more deaths from tumour in those patients with moderate or high pleomorphism. Patients with low pleomorphic tumours could be successfully treated by endoscopic methods and none of them had radiotherapy or came to cystectomy.

The prognosis for tumours invading the lamina propria was significantly worse, even though many of these patients had radiotherapy. We had little success in the control of tumours with Epodyl or Thiotepa.

Multiple tumours did just as well as single ones in the overall survival but many more of them had radiotherapy and cystectomy. However, it is significant that those patients with multiple tumours without lamina propria invasion could be controlled endoscopically and none had radiotherapy or cystectomy.

Anderson (1973) and Pomerance (1972) also found that multiple tumours did as well as single ones. Patients with multiple tumours presented sooner than those with single ones, as did those patients whose tumours showed moderate differentiation, pleomorphism and mitotic rate. This is different from Miller *et al.* (1969), who found that patients with multiple tumours presented earlier than those with single tumours.

50% of the patients with single tumours became tumour free compared with 30% of those with multiple tumours. Nearly 20% of patients with single tumours developed multiple recurrences compared with 44% in the multiple group. There was no evidence that these were due to transurethral resection and there was also no evidence that transurethral resection caused dissemination of the tumour outside the bladder as suggested by Wallace (1973). Most of the recurrences were of tumours with similar histology but 7·8% developed invasive tumours. The prognosis for these patients was bad, and their invasive tumours often developed quite unexpectedly. The histological

Table IX

T1 Bladder Tumours 1977.
Overall Survival at 3 years and 5 years ( )%

	Sheffield 1977	Anderson 1973	Pryor 1973	Miller 1969	Pomerance 1972
Survival	83·2 (71·8)	73·0	77·0	(84·4)	88·6 (77·0)
Tumour death	3·6 (4·2)	–	9·6	(2·8)	9·0
Other death	6·0 (7·8)	–	3·25	(12·8)	–

characteristics in the original tumour in these patients were adverse with a high pleomorphism and mitotic rate.

56·9% of the patients lived longer than 5 years and only 3·2% of them subsequently died of their tumour. 10·5% died of other causes and 21% of them still retained some bladder tumour but had little morbidity from it.

We do not think there is any need to alter our treatment of these T1 lesions by transurethral resection, but those tumours showing invasion into the lamina propria and high or moderate pleomorphism should be treated as invasive tumours of a higher stage. This applies particularly to multiple tumours and we should undertake cystectomy much earlier. The results of cystectomy are good and the mortality in selected patients should be low.

Summary

167 patients with T1 bladder transitional cell tumours treated by transurethral resection or cystodiathermy are reviewed.

The overall crude survival was 83·2% in 3 years and 71·8% in 5 years.

7·8% of the patients developed an invasive tumour and these patients had an unfavourable initial tumour with moderate or poor differentiation and high or moderate mitotic rate. High or moderate pleomorphism was particularly unfavourable.

Multiple tumours did as well as single ones but more of them had invasion of the lamina propria and a larger number were treated by either radiotherapy or cystectomy.

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The Authors

J. L. Williams, FRCS, Consultant Urologist.
J. C. Hammond, FRCS, Senior Registrar (now Consultant Urologist, Plymouth).
N. Saunders, FRCS, Registrar.

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A Toxicity Study of the Treatment of T3 Bladder Tumours with a Combination of Radiotherapy and Chemotherapy

R. W. GLASHAN, A. L. HOUGHTON and M. R. G. ROBINSON

Huddersfield Royal Infirmary, Huddersfield; The University of Leeds, Leeds; Pontefract General Infirmary, Pontefract; and Members of the Yorkshire Urological Cancer Research Group[1]

The results of local treatment of transitional cell carcinoma invading bladder muscle are disappointing. Survival of category T3 patients at 5 years is not more than 33% whether the initial treatment is surgery, radiotherapy or a combination of the two. Jewett (1970) quoted 5-year survival figures of 16-28% for B2 tumours, while Edsmyr (1975) and Wallace and Bloom (1976) quote figures of 25% and 21% respectively for T3 tumours. These figures are not significantly improved by combining the two modalities (Wallace and Bloom, 1976). Many patients with T3 tumours die of metastatic disease (Rider and Evans, 1976).

In 1976 the Yorkshire Urological Cancer Research Group reported an objective remission in 7 out of 20 patients using a combination of adriamycin and 5-fluorouracil confirming the results of previous studies using these drugs singly (Carter and Wasserman, 1975).

There is experimental evidence that chemotherapy is more effective when the tumour mass is small (Martin and Fugmann, 1960; Martin, Fugmann and Hayworth, 1962; Wilcox *et al.*, 1965), a fact strongly emphasised by Burchenal in his James Ewing lecture on adjuvant therapy (1976).

It is, therefore, appropriate to determine whether chemotherapy given shortly after primary treatment by radical radiotherapy to patients with category T3 bladder cancer without metastases (*i.e.* T3 NX MO) confers any benefit. Before commencing such a trial of adjuvant chemotherapy a preliminary toxicity trial was carried out in order to assess whether the combination of radical radiotherapy and chemotherapy is safe and can be tolerated by the patient. No attempt has been made in this study to evaluate overall therapeutic results.

Patients

18 patients with histologically proven transitional cell bladder tumours were entered into the study; there were 14 male and 4 females, mean age 65 years (range 44-76). All were T3 category. The presence of metastatic disease was not specifically sought. Patients with additional primary tumours, serious intercurrent disease, renal failure, liver disease, impaired bone marrow, peptic ulceration, uncontrolled infection, or who were senile were excluded.

Methods

Adriamycin (50 mg/m^2) and 5-fluorouracil (500 mg/m^2) were given at 3 weekly intervals, 1 to 3 months following the completion of radical radiotherapy to the bladder. The drugs were given into the side arm of a fast-running intravenous infusion. This regime was followed unless there were signs of toxicity, in which case modifications of the dose or time interval between cycles

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[1] L. Campbell-Robson, P. Corbett, N. Cowley, R. J. Cross, H. G. Frank, B. Richards, E. Rowe, P. H. Smith.

were made. Heart failure was an indication for the cessation of therapy. Previous experience (Lefrak *et al.*, 1973; Cortes *et al.*, 1975) has shown that the cardiomyopathy and heart failure due to adriamycin are uncommon provided that the total dose does not exceed 550 mg/m^2; above this dose the incidence rises steeply. For this reason none of our patients received more than 550 mg/m^2 of adriamycin.

Both treatment and follow-up were carried out on an out-patient basis. The patients were reviewed weekly and specific enquiries were made about gastrointestinal and cardiovascular symptoms. The oral cavity was inspected for signs of stomatitis or ulceration. A full blood count was performed weekly and tests of renal and liver function every third week. An electrocardiogram was done immediately before each cycle of therapy. Patients were assessed at 12 weeks (*i.e.* after 4 cycles) for:

(*a*) Combined toxic effects.
(*b*) The clinical stage of the disease. If there was progression of the primary tumour alternative treatment was given as deemed necessary by the responsible clinician.

Results

No patient received less than 4 cycles, and 3 tolerated as many as 11 cycles (mean 7·5 cycles). For various reasons 11 patients discontinued chemotherapy before the maximum dose could be given. Of these, 3 patients died, 3 patients showed evidence of disease progression and received alternative treatment and 5 developed toxicity. Of the deaths, 1 was due to carcinomatosis, 1 to pulmonary embolus following cystectomy for a contracted bladder and 1 to broncho-pneumonia and congestive cardiac failure (possibly attributable to 9 cycles of cytotoxic therapy).

Toxicity (Table)

The haematological effects were not severe. Although the haemoglobin level tended to fall by about 1-2 gm/dl over 4 cycles, only 1 patient required a blood transfusion because of anaemia. There was a predictable fall in the leucocytes and platelets, with a nadir at 2 weeks. The total white count sometimes fell below 4,000 per ml but in only 2 patients was it necessary to postpone and modify subsequent doses of chemotherapy. In no patient did the platelet count fall below 100,000 per ml. Cardiotoxicity was found in 4 patients. 2 patients developed minor abnormalities (transient ST-T changes in 1 and atrial fibrillation controlled with digitalis in another). Both continued treatment. A third patient developed clinical heart failure and a right bundle branch block after 8 cycles and was withdrawn from the study. The fourth patient, a woman of 66 years, received 9 cycles without apparent ill effect, but was later admitted to a medical ward with broncho-pneumonia and congestive heart failure. She died, and her death was possibly related to chemotherapy. Although all patients suffered some form of gastrointestinal side-effects this was

Table

Toxicity in 18 Patients

Haematological		
Haemoglobin	1	transfused
WBC	2	dose modified
Cardiac	4	(*a*) temporary ST-T changes
		(*b*) atrial fibrillation
		(*c*) heart failure—RBBB
		(*d*) refractory heart failure
Gastrointestinal	4	declined further treatment
Alopecia	18	(100%)

usually of a mild degree and short duration. However, the severity of the symptoms became worse with each successive cycle and 4 patients eventually declined further chemotherapy after 4, 4, 5 and 8 cycles, respectively, despite partial relief with anti-emetics. There were no significant changes in liver function tests attributable to the combined therapy. All patients suffered from alopecia which recovered when treatment ceased, and in some cases the hair began to grow before the full course of chemotherapy had been given.

Discussion

The purpose of this study was to determine whether the toxicity due to the combination of radical radiotherapy followed by chemotherapy with adriamycin and 5-fluorouracil is acceptable and whether this combination is suitable for use in a controlled trial of adjuvant chemotherapy. No patient developed serious subjective or objective signs of toxicity during the first 4 cycles, but increasing problems arose with continued treatment. 4 patients declined chemotherapy after 4 cycles because of nausea and vomiting and 2 patients developed congestive heart failure, presumably the result of adriamycin induced cardiomyopathy. In 1 this was fatal.

Conclusions

These results suggest that the use of adriamycin and 5-fluorouracil as an adjuvant to radical radiotherapy is safe. All the patients tolerated 200 mg/m^2 of adriamycin and 2 g/m^2 of 5-fluorouracil without significant toxicity. The value of such treatment should be tested by a randomised trial of adjuvant chemotherapy following radical radiotherapy given as primary treatment to patients with category T3 bladder tumours.

Summary

18 patients with category T3 bladder cancer were treated with a combination of radical radiotherapy followed after an interval of 1-3 months by pulsed chemotherapy with adriamycin and 5-fluorouracil.

Providing the chemotherapy was limited to 4 cycles, there was no serious toxicity and the regime was well tolerated.

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The Authors

R. W. Glashan, FRCS(Ed), FRCS(Glas), Consultant Urological Surgeon, Huddersfield Royal Infirmary.
A. L. Houghton, FRCS, Clinical Research Fellow, University of Leeds.
M. R. G. Robinson, FRCS, Consultant Urological Surgeon, Pontefract General Infirmary.

Requests for reprints should be sent to: Mr M. R. G. Robinson, Department of Urology, Pontefract General Infirmary, Pontefract.

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The Treatment of Advanced Bladder Cancer with Methotrexate

A. G. TURNER, W. F. HENDRY, GRANT B. WILLIAMS and H. J. G. BLOOM
Departments of Urology and Radiotherapy, Royal Marsden Hospital, Fulham Road, London, S.W.3

Methotrexate was first used for bladder cancer by Sullivan (1962), who gave it intra-arterially and noted "a sustained clinical benefit and decrease in tumour size". Other reports by Andrews and Wilson (1967), Pavone-Macaluso (1971) and Altman *et al.* (1972) also suggested that methotrexate could be of value but the numbers in each series was small. Collectively these and several other papers gave a response rate of about 36%. The first large series was by Hall *et al.* (1974), who found an objective response rate of 26% in a study of 42 patients at this hospital.

This paper extends the report of Hall *et al.* (1974) and includes the overall experience of the use of methotrexate in varying regimes at the Royal Marsden Hospital over a period of 7 years, 1970-1977.

Patients

Patients with advanced local disease that did not respond to radiotherapy or had recurred after radiotherapy, and patients with metastatic disease, were considered for methotrexate therapy. Prior to treatment each patient was assessed as follows: Hb, WBC, platelets, urea, glomerular filtration rate (GFR), EDTA or creatinine clearance, chest X-ray, bone scan. As methotrexate is excreted through the kidney, renal function was always carefully assessed prior to administration of the drug.

Methods

During the period under consideration 3 different regimes were used. All regimes were given every 2 weeks (Table I).

A. Methotrexate 50 mg intravenously } without folinic acid rescue, given as an outpatient.
B. Methotrexate 100 mg intravenously }
C. Methotrexate 200 mg intramuscularly with folinic acid rescue (21 mg i.m.) at 6, 12 and 24 hours given as an in-patient.

If the glomerular filtration rate was less than 80 ml/min the dose of methotrexate was reduced. After the initial investigations had been performed, the only investigations performed prior to each subsequent dose were a WBC and a platelet count. If the WBC count was less than $3 \times 10^9/l$ and/or the platelet count was below 100,000 $10^9/l$ then the dose was not given and the counts were re-checked 2 weeks later.

Toxic side-effects, such as mucositis or skin reactions were recorded. If mild, no further chemotherapy was given until recovery occurred, but if severe then the treatment was abandoned.

Tumour parameters were measured after every 3 months of treatment and results assessed.

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Results

During the period 1970-1977, 61 patients were treated with 1 of the regimes outlined. Patients who had received only 1 or 2 courses of treatment before death were excluded. All these patients died of terminal disease and *not* of methotrexate toxicity.

Only objective responses are considered and are divided into 2 categories:

(1) Complete. Complete regression of tumour lasting at least 6 months.
(2) Partial. Objective reduction in size of metastatic deposits as seen radiologically and/or down staging of bladder tumour assessed under general anaesthetic and confirmed by more than one observer.

Examples of complete regression of lung deposits may be seen in the Figure.

Complete objective response was noted in 3 patients receiving the 100 mg dosage and in 1 patient receiving 200 mg. The site and duration of the complete responses are shown in Table II. No complete responses were noted with the 50 mg dose. The patient receiving the 100 mg dose who had a complete objective response in bone is still alive: after being paralysed and unable to walk, he is now back at work. The patient receiving the 200 mg dosage had a complete lung response but died of bony disease; methotrexate had been discontinued when the lungs remained clear, but after cessation, a spinal deposit developed and the patient deteriorated and died; the lungs remained clear at death.

Partial objective response was observed in a larger number of patients (Table III). Several of these patients are still alive, and although at present classified as partial response may become complete. The patient who has survived for 67 months was originally staged T3, but after radiotherapy was at laparotomy staged T4 and totally inoperable due to fixation. 67 months later, the patient is still alive and the fixation is reduced.

A summary of the results (Table IV) shows that there is a variation in the response rate according to dosage and that up to 56% objective response rate may be achieved using methotrexate. Besides the objective response the subjective response of pain relief was noted in 5 patients. This is not considered in the assessment of the value of methotrexate therapy but in several patients it was a very noticeable response despite no objective evidence of decrease in size of metastatic disease. Side-effects were divided into mild and severe, and are shown in Table V. In mild cases, therapy was discontinued until recovery; in effect, this was usually by the omission of only one dose. Severe reactions caused the abandonment of treatment and was noted in very few patients. Skin necrosis was only observed in one case when radiotherapy was given concurrently.

Discussion

Carter and Wasserman (1975), after reviewing the published reports on chemotherapy for advanced bladder cancer, concluded that there were only 3 agents of proven value: adriamycin, mitomycin C

Table I

Patients Treated and Courses Received

	Methotrexate every 2 weeks		
	50 mg	100 mg	200 mg with rescue
Number of patients treated	23	22	16
Courses received	3-47 av. 10·9	3-48 av. 14·5	3-49 av. 13·0

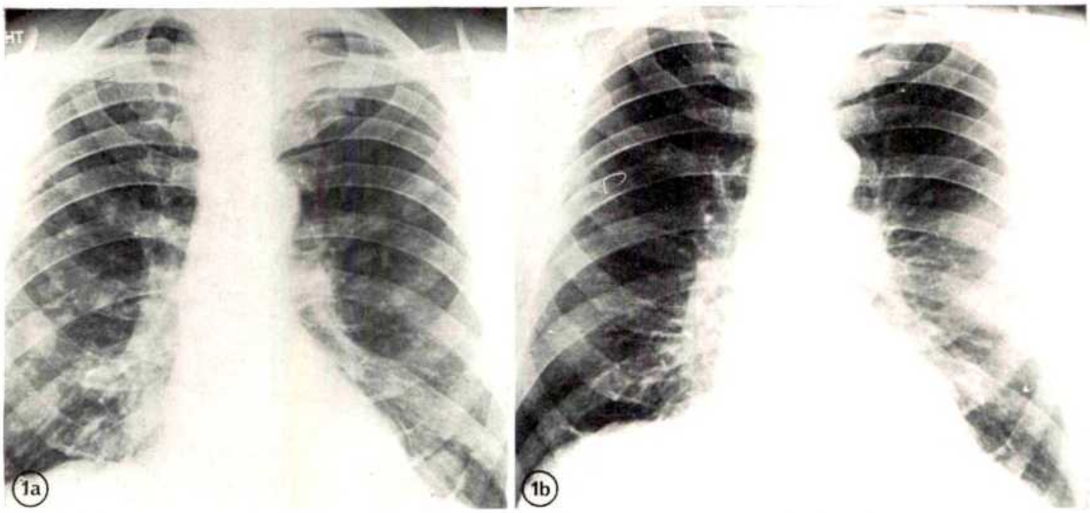

Fig. Complete response. Chest X-ray. (i) Metastases present pre-treatment. (ii) Metastases absent post-treatment.

and 5-fluorouracil. This present study suggests that methotrexate should be added to that list, the observed response rate of 56% being greater than that published for any other drugs.

Experience has been gained on the use of methotrexate, its dosage, response rate and toxicity. Pre-treatment assessment of renal function is essential as methotrexate is excreted through the kidney. 43% of the dose is excreted within the first hour and most after an intravenous dose within 12 hours (Freeman, 1958). In patients with reduced renal function, a single injection may give plasma levels comparable to a 24-hour continuous infusion (Price, 1977). This is important because Miller *et al.* (1961) and Goldie, Price and Harap (1972) showed that toxic effects depended on length of time of exposure rather than the size of the dose. Furthermore, methotrexate itself can cause impaired renal function by tubular damage (Condit, Chares and Joel, 1969) and so renal function must be re-checked during therapy. With the regimes used in this study, however, depression of renal function was never observed.

Initially, to gain experience in the use of methotrexate, the low dose of 50 mg was used without folinic acid rescue. This was planned to be given weekly but because of the high incidence of

Table II

Complete Objective Response: Duration of Remission in Months at Sites Shown

Complete objective response	Duration of remission in months (Methotrexate every 2 weeks)		
	50 mg	100 mg	200 mg with rescue
Local	–	–	–
Lung	–	7	20
Bone	–	6	–
Skin	–	7	–
Total numbers	0/23	3/22	1/16

Table III

Partial Objective Response: Duration of Remission in Months at Sites Shown

Partial objective response	Duration of remission in months (Methotrexate every 2 weeks)		
	50 mg	100 mg	200 mg with rescue
Local	67	4, 7, 14	4, 6, 24
Nodal	–	3	4
Lung	2	4, 8, 12	4, 3, 4
Bone	–	2, 4, 14	3, 3
Skin	2	3	–
Total numbers	3/23	9/22	7/16

Table IV

Overall Response Rate

Objective response	Methotrexate every 2 weeks		
	50 mg	100 mg	200 mg with rescue
Partial	3/23	9/22	7/16
Complete	0/23	3/22	1/16
Overall response rate	3/23 = 13%	12/22 = 56%	8/16 = 50%

neutropenia and mucositis, the practical dose regime became every 2 weeks. The incidence of postponed doses due to neutropenia was reduced, and it has been shown recently (Harding *et al.*, 1977) that although the incidence of neutropenia is reduced if each course is separated by over 8 days, the antitumour effect is not altered.

The response rate with the 50 mg dose was poor and the dose was increased to 100 mg and 200 mg, but with the latter a folinic acid rescue was necessary. Response rates between the 2 higher doses are not significantly different, which most probably reflects the use of the rescue procedure giving an equally effective exposure time to methotrexate. It is, however, an important fact as it shows that the drug may be given effectively on an out-patient basis.

Methotrexate is a well-tolerated chemotherapeutic agent with few of the more unpleasant side-effects noted with other agents. Apart from neutropenia and mucositis which respond well to oral hygiene and topical folinic acid, the only other side-effect noted was nausea, which was treated effectively with metaclopromide 10 mg before the injection and 4-hourly p.r.n. afterwards. Hepatotoxicity has been recorded but no cases were found in the series; cardiotoxicity, an important effect when considering the age of the bladder cancer population, has not been recorded with methotrexate.

Long-term methotrexate use has been studied in children receiving the drug for lymphocytic leukaemia and its toxic effects, both acute and chronic, have been noted by Nesbit *et al.* (1976), who found serious side-effects in hepatic, pulmonary and skeletal systems. In our study, only 1 person developed a pulmonary problem (see Table V) but that was an early rather than late

Table V

Toxic Side-effects

Toxicity	Methotrexate every 2 weeks 50 mg	 100 mg	 200 mg with rescue
Mild (missed a dose)			
Mouth ulcers	9/23	8/22	–
Skin rash	1/23	–	–
Severe (treatment abandoned)			
Marrow toxicity	–	–	1/16
Lung perfusion defect	–	–	1/16
Severe mucositis	1/23	1/22	–
Skin necrosis	–	1/22	–

effect. The concurrent use of methotrexate and radiotherapy is dangerous and the case of skin necrosis was in a patient receiving both radiotherapy and methotrexate.

It can be concluded that methotrexate is a valuable chemotherapeutic agent in the management of advanced bladder cancer. It can be used safely and effectively on an out-patient basis and has few serious side-effects. It may be a useful agent in future combined modality treatment for advanced bladder cancer to eliminate micrometastases outside the irradiation field (Wallace and Bloom, 1976).

Summary

61 patients with advanced bladder cancer were treated with methotrexate. 3 different regimes were used, 2 given on an out-patient and 1 on an in-patient basis. A response rate of 56% was found in patients who received 100 mg of methotrexate intravenously every 2 weeks as an out-patient.

Provided that renal function is checked before therapy and is normal, then methotrexate can be used safely; it being well tolerated and having few serious side-effects.

We would like to thank Dr L. A. Price, Senior Lecturer in Medicine and Honorary Consultant Physician at the Royal Marsden Hospital, for his advice on the use of methotrexate.

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The Authors

A. G. Turner, BSc, FRCS, Lecturer in Urology.
W. F. Hendry, ChM, FRCS, Consultant Urologist.
Grant B. Williams, MS, MSc, FRCS, Consultant Urologist.
H. J. G. Bloom, MD, FRCP, FRCR, FACR, Chairman of the Department of Radiotherapy and Oncology.

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Scottish Prostates: a 6-Year Review

ANDREW G. GRAHAM
Western Infirmary and Royal Hospital for Sick Children, Glasgow

Since 1967, consultants in Scottish hospitals have received annually a computer-based summary of statistical data of all patients admitted under their care, namely, the Scottish Consultant Review of In-patient Statistics (SCRIPS), issued initially by the Research and Intelligence Unit of the Scottish Home and Health Department (Parkin, Clarke and Heasman, 1976). Apart from statistics about the quantity, nature and outcome of his own work, SCRIPS also provides data on the average experience of consultants in the same specialty at national level, in the hope that this will enable each consultant to compare the results of his personal practice with those of his colleagues. It was hopefully suggested that one benefit of such study might be an "improvement in the service given or more efficient utilisation of hospital facilities".

This review of the operation of prostatectomy in Scotland is based on the SCRIPS returns for the 6-year period 1969-1974, the last year for which figures have been issued.

Patients and Methods

The trends in prostatectomy are reviewed under 6 main headings: the number of patients, the type of operation, mortality rate, age of patient, form of admission (emergency or elective), and duration of stay in hospital.

Prostatectomies performed by general surgeons are not included in this review, although efforts to provide the data are being made by the Information Services Division of the Scottish Health Service Agency.

Results

(a) Number of Prostatectomies

During the first 4 years of the review the total number of operations per annum rose from 1,038 to 1,647, and thereafter remained fairly constant (Table). There was virtually no change in the number of urological beds in Scottish hospitals throughout this time.

(b) Type of Operation

Figures are given in the Table for the 3 principal forms of prostatectomy employed—suprapubic (SP), retropubic (RP) and transurethral (TUR). During the first 4 years there was a fairly steady increase in all 3 forms of operation, and thereafter a sharp drop in the proportion of both "open" forms of operation while TUR's continued to rise.

(c) Mortality Rate

The percentage mortality rate for each form of operation is given in the Table. For TUR's and retropubic prostatectomy the overall rate of 1·4 and 1·8 % compares favourably with figures from other centres (Singh, Tresidder and Blandy, 1973), and the general trend is downwards. For

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suprapubic prostatectomy, however, the overall rate is 3·6%, with figures of 4·1% for 1972 and 5·2% for 1974. Were it not for this last figure, the general pattern for all forms of prostatectomy, other than in 1970, would be one of gradual improvement in the mortality rate.

(d) Age of Patient

SCRIPS only provides data about the proportion of patients over 65 years old (Fig. 1). In 1969 the figure was 65%, with a steady rise to 72% in 1974.

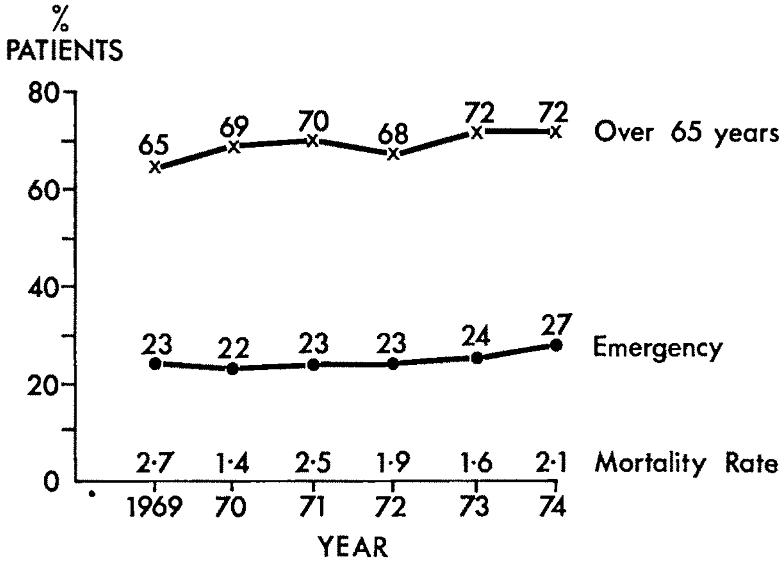

Fig. 1. Prostatectomy in Scotland 1969-74. Graph showing percentage of patients over 65 years old and admitted as emergency. The mortality rate for all forms of prostatectomy during each year is included.

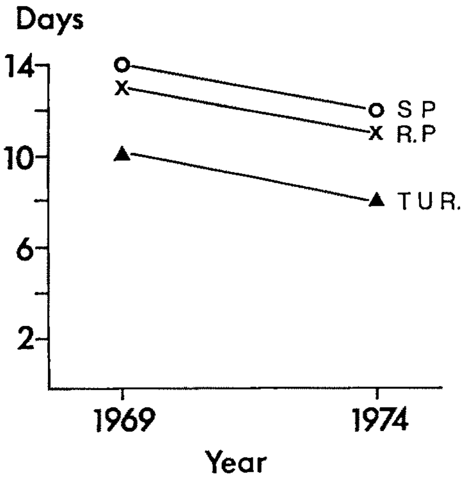

Fig. 2. Prostatectomy in Scotland 1969-74. Mean duration of postoperative stay. SP—suprapubic, RP—retropubic, and TUR—transurethral prostatectomy.

(e) Emergency Admissions

The proportion of patients admitted as emergencies (Fig. 1) remains remarkably constant at 22-24% throughout the series, with a rather sharp increase in 1974 to 27%. Closer scrutiny in this increase revealed the interesting point that it was due entirely to an isolated rise in the *suprapubic* emergency admission rate (35%), *i.e.* in the same year as the peak mortality rate of 5·2% in this group.

(f) Duration of Hospital Stay

SCRIPS provides figures only of the mean duration of postoperative stay (Fig. 2). In each form of prostatectomy the postoperative stay has been reduced by 2 days during the period of review, TURs enjoying a significant 3-day advantage over the open operations.

Discussion

Although the population of Scotland is diminishing slowly, there is still an increase in the age-group likely to require prostatic surgery, and the numbers in the review bear out this trend. The levelling-off of total numbers of prostatectomy in 1972-1974 may well reflect the inability of urologists to cope with a growing demand for elective prostatic surgery, due to the failure of the expansion of urological beds within the hospital service. The increase in prostatic emergencies in 1974 could be interpreted as an indication that patients with prostatic disease are having to wait longer for surgery and therefore running an increased risk of retention of urine or haemorrhage. That emergency admission carries with it a significantly higher mortality rate after prostatectomy is well recognised. Ashley, Howlett and Morris (1971) recorded a 3% mortality rate after emergency admission compared with less than 1% for planned surgery. In the present review the association of a rise in the 1974 mortality rate for suprapubic prostatectomy and the increased proportion of emergency admissions in this group has already been noted.

The steady increase in TURs in Scotland would appear to confirm trends elsewhere. The obvious attractions of a lower mortality rate and a shorter stay in hospital are now widely accepted by urologists and need not be restated here. It is perhaps interesting to note that the proportion of TURs in Scotland in 1974 was still only 66%, whereas Argyrou *et al.* (1974) claimed that about 90% of prostatectomies in urological centres were done transurethrally. In our own urological department at the Western Infirmary, Glasgow, 748 (73%) out of 1,025 prostatectomies during 1974-1976 were TURs compared to 91 (45%) out of 198 in 1969. There seems little doubt that the swing towards transurethral surgery is both continuing and desirable, particularly in view of the heavy demands on urological beds.

Table

Form of prostatectomy		1969	1970	1971	1972	1973	1974	Total
Suprapubic	No.	153	134	266	340	290	245	1,428
	% Mortality	2·7	2·3	2·7	4·1	2·7	5·2	3·6
Retropubic	No.	200	200	264	357	311	275	1,607
	% Mortality	2·5	3·0	1·6	1·6	1·4	1·5	1·8
TUR	No.	685	774	770	950	913	1,098	5,190
	% Mortality	2·8	0·9	2·3	1·3	1·4	1·5	1·4
Total	No.	1,038	1,108	1,300	1,647	1,514	1,618	8,225
	% Mortality	2·7	1·4	2·5	1·9	1·6	2·1	2·0

Conclusions

It would be unwise to draw hard conclusions from a review of this nature; the statistics themselves are open to error at source, in presentation and in interpretation. Despite these reservations, it may be fair to state the following:

1. There is no evidence of any diminution in the demand for prostatectomy in Scotland.
2. There is a steady increase in the use of transurethral as opposed to "open" surgery.
3. Transurethral prostatectomy has a consistently lower mortality rate than open prostatic surgery.
4. It would seem unwise to reduce either the number of beds presently set aside for the specialised management of prostatic disease, or the numbers of urologists in training in Scotland.
5. The provision of data in SCRIPS form can provide the clinician with information enabling him to influence possible improvements in the hospital service and in his own practice.

Summary

A review of all prostatectomies performed by urologists in Scotland during 1969-1974 is presented.

Factors influencing the mortality rate are discussed and the steady increase in low-mortality (1·4%) transurethral prostatectomy noted.

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The Author

Andrew G. Graham, FRCSE, Consultant Urologist.

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Potency and Prostatectomy

T. B. HARGREAVE and T. P. STEPHENSON

The Western Infirmary, Glasgow; The Middlesex Hospital, London; University College Hospital, London; Edgeware General Hospital, Middlesex

There is considerable folk-lore concerning sexual potency and the operation of prostatectomy. Many men regard prostatectomy as the end of their sexual life and in younger men this may add to preoperative anxiety; some are unaware of the possibility that impotence may result. It is worth noting that as a result of accurate diagnostic urodynamic techniques, prostatectomy is increasingly indicated to relieve symptoms in younger men. Older men sometimes feel inhibited about asking advice, believing that at their age any sexual potency is improper.

A postoperative decrease or absence of sexual potency has been reported in between 5% and 40% of men subjected to transurethral resection (Holtgrewe and Valk, 1964; Finkle and Prian, 1966).

The present study was undertaken to try to assess the incidence of post-prostatectomy impotence.

Method

This was a prospective questionnaire study with a 6-month follow-up. The first questionnaire about the preoperative state was completed by the patient before leaving hospital; the second questionnaire was sent by post 6 months later. A record of the type of operation, the histology and any relevant major illness was obtained from the hospital notes. Anonymity was preserved throughout the study.

The questionnaire related both to the urinary state and to sexual performance (Table I). For the purpose of this analysis a man was regarded as fully potent if he answered the 4 questions about sexual function in the affirmative and impotent if the 4 questions were answered negatively; the "additional comments" column in the questionnaire was particularly helpful in the assessment of men reporting partial potency.

Patients

The men were treated at 4 hospitals. 2 of these were teaching hospitals with specialist departments of urology, 1 was a teaching hospital without a specialist department, and 1 was a district general hospital. The operations were performed by the staff of the units concerned. Thus 113 men had a transurethral resection, 44 a retropubic operation, 43 a transvesical prostatectomy and 52 a reconstructive retropubic posterior prostatectomy (Turner-Warwick, 1969).

Men with known carcinoma of the prostate, those who because of great age or frailty were unable to answer sensibly, and those who did not wish to participate, were excluded from the study. 252 men completed both questionnaires and had adequate records in the hospital notes. A further 61 men were excluded; 13 died within the 6-month period, 7 had inadequate or untraceable hospital notes and 41 were lost to follow-up.

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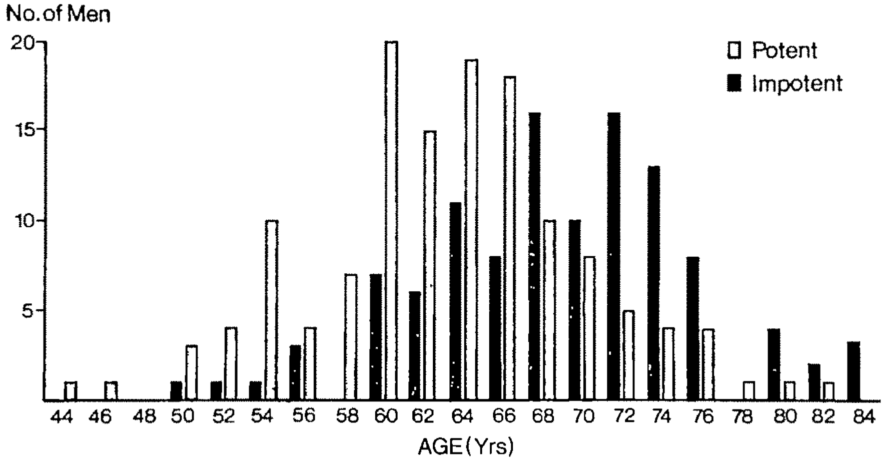

Fig. 1. 252 men: age and sexual potency.

Results

Age and Sexual Potency

The age and sexual potency in 252 men before operation is shown in Fig. 1.

The average age of the men was 66.5 years with the youngest aged 45 and the oldest 84. The mean age of the potent men was 63 years and of the impotent men 70 years.

Effect of Prostatectomy on Potency

Men with Full Preoperative Potency

98 men reported full potency before their prostate operation. 1 of these men was started on stilboestrol after prostatectomy because of carcinoma of the prostate. The effect of prostatectomy on the remaining 97 men is shown in Table II.

Men with Impaired Preoperative Potency

44 men reported partial preoperative potency. 3 of these men were started on stilboestrol after prostatectomy and a fourth man developed severe heart disease. The effect of prostatectomy on the remaining 40 men is shown in Table III.

Improved Potency

4 men reported improvement in potency after operation (Table IV).

Effect of Prostatectomy on Ejaculation

90 men were potent before operation and experienced no change in potency thereafter. The effect of prostatectomy on ejaculation in this group was recorded (Table V).

Impotence and Duration of Prostatic Symptoms

106 men were impotent before and after operation. 16 of these men had other disease sufficient to cause impotence. Of the remaining 90 impotent men, 66 completed enough questions to allow further analysis of the relationship between the duration of urinary symptoms and of impotence (Fig. 2).

Benefit from Prostatectomy and Potency

The men were asked to comment on whether the prostatectomy had helped them or not and their replies and potency state were received (Table VI). This shows that any worsening of potency did not prejudice patients when assessing benefit to micturition of their operation.

Discussion

In this series the average age at the time of prostatectomy was 66·5 years and 57% of these men claimed to be fully or partially potent preoperatively. Finkle *et al.* (1959) reported a 65% potency rate in men under 69 years. These rates suggest patients may need information about the effects that prostatectomy may have on potency.

The incidence of total impotence which followed prostatectomy in this study was 4% if the man was fully potent preoperatively but was much higher if there was failing preoperative potency. This result is low when compared with 40% impotence reported by Holtgrewe and Valk (1964) but agrees with a more recent objective study using penile plethysmography (Madorsky *et al.*, 1976) where no case of total impotence was found in 14 men potent preoperatively. Penile erection depends on appropriate psychological and general well-being, an intact spinal cord, intact autonomic nerves to the penis, and normal erectile tissues with an adequate blood supply. It is difficult to understand why careful prostatectomy (excluding the perineal operation) should affect these mechanisms any more than a major operation such as partial gastrectomy. In the "comments" column several of our patients said they were afraid to try intercourse and attributed total or partial impotence to this fear. Zohar *et al.* (1976) found that all potent patients who were given a preoperative explanation about sexual function remained potent postoperatively but not so when no explanation was given. Possibly our rates of impotence would have been even lower if all patients had been counselled.

One-third of the potent men had continued postoperative ejaculation and this was most marked after transurethral resection. This emphasises that prostatectomy should not be regarded as a contraceptive operation unless vasectomy has also been done. There is some doubt about the

Table I

Questions asked about Potency

Do you get satisfactory erections of the penis for sexual intercourse?	Yes/No
Do you get ejaculation of sperm?	Yes/No
Do you get a satisfactory orgasm (sensation at the climax of the sex act)?	Yes/No
Do you still experience the desire for sexual intercourse?	Yes/No

Table II

Effect of Prostatectomy on 97 Men with Full Preoperative Potency

Operation	Preoperative full potency	Postoperative reduced potency	Postoperative impotence
TUR	44	1	2
TV	14	1	–
RP	16	1	–
RRPP	23	–	2
	97	3 (3·1%)	4 (4·1%)

accuracy of this observation. A properly performed reconstructive retropubic posterior prostatectomy opens the prostatic cavity and reconstructs it so widely that the verumontanum (which is preserved in this procedure) lies within the bladder cavity (Turner-Warwick *et al.*, 1973); it is almost inconceivable that such patients actually ejaculate any significant volume although they often get the sensation of doing so. The significantly high incidence of ejaculation after transurethral resection raises some doubt about the completeness of the resection in some cases.

4 men reported improved potency. 3 of these who achieved full postoperative potency were young and had a short duration of urinary symptoms and impotence.

There was an interesting correlation between the duration of prostatic symptoms (poor stream) and of impotence ($P < 0{\cdot}001$) and this was not explained by age. Low plasma testosterone levels have been reported in elderly men with prostatic hyperplasia (Horton *et al.*, 1975) and there is much current speculation about the part hormone levels may play in the genesis of prostatic hyperplasia and impotence.

Table III

Effect of Prostatectomy on 40 Men with Partial Preoperative Potency

Operation	Preoperative partial potency	Postoperative reduced potency	Postoperative impotence
TUR	17	1	2
TV	6	4	–
RP	11	1	1
RRPP	6	3	1
	40	9 (22·5%)	4 (10%)

Table IV

Improved Potency after Prostatectomy

Operation	Age	Duration of urinary symptoms	Preoperative potency	Postoperative potency
TUR	63	2 years	Partial 2 years	Full
TUR	66	6/12	Impotent	Full
RP	62	1	Partial 6/12	Full
SV	74	6/12	Partial 5 years	Improved

Table V

Postoperative Ejaculation in 90 Men

	Postoperative ejaculation		
Operation	Full	Reduced	Absent
TUR	18	1	22
TV	4	–	9
RP	3	–	12
RRPP*	5	–	16
	30	1	59

* Vasectomy routinely performed.

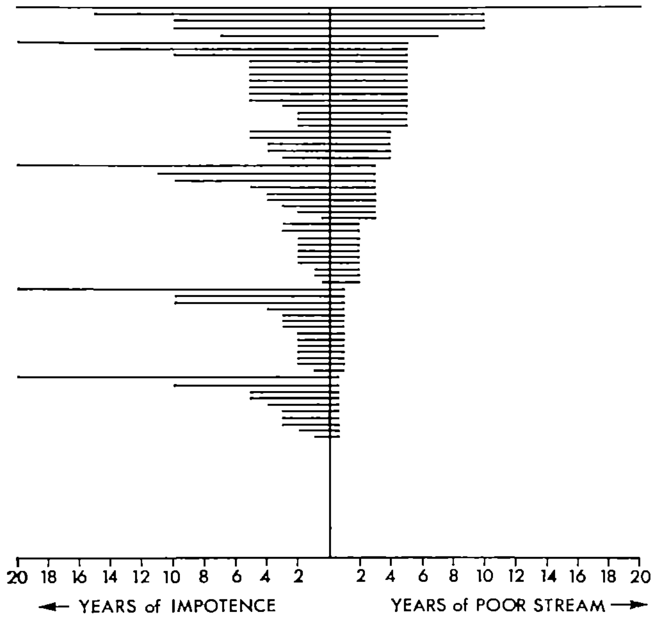

Fig. 2. Correlation between impotence and urinary symptoms.

95% of the men in this series reported benefit from their prostatectomy and this assessment was not altered when potency was impaired. An analysis of the urinary symptoms of the series of patients before and after operation will be published separately.

Summary

A prospective questionnaire study with a 6-month follow-up was carried out to determine the incidence of post-prostatectomy impotence.

57% of patients were potent at the time of operation. A man with full potency had a 4% chance of becoming totally impotent and a 3% chance of becoming partially impotent. A man with failing preoperative potency had a 10% chance of becoming totally impotent and a 22% chance of becoming worse.

No particular method of operation was at fault. One-third of potent men claimed to have some postoperative ejaculation.

Table VI

Benefit from Prostatectomy related to Potency

		Benefit from prostatectomy				
No. of men	Potency	++	+	0	–	––
117	Unchanged potency	99	14	3	–	1
4	Improved	4	–	–	–	–
25	Worsened	23	1	1	–	–
106	Unchanged impotence	77	21	5	3	–

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The Authors

T. B. Hargreave, FRCSE, Senior Urological Registrar, Western Infirmary, Glasgow.

T. P. Stephenson, FRCS, Senior Urological Registrar, Middlesex Hospital (now Consultant Urologist, Cardiff Royal Infirmary).

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Continuous Irrigation of the Bladder after Prostatectomy: Its Effect on Post-prostatectomy Infection

J. R. G. BASTABLE, R. N. PEEL, D. M. BIRCH and B. RICHARDS
York District Hospital, York

Post-prostatectomy complications, especially epididymo-orchitis and secondary haemorrhage, are more common if there is bacterial infection of the urine.

Bacteriuria after catheterisation can be prevented in some cases by the use of urethral antiseptics prior to instrumentation (Mitchell, Slade and Linton, 1962; Gillespie *et al.*, 1962), of antiseptic irrigation solutions at cystoscopy (Lytton, 1961), and of closed systems of bladder drainage and the instillation of antiseptics into the urine drainage receptacle (Gillespie *et al.*, 1964; Roberts *et al.*, 1965; Webb and Blandy, 1968).

Disappointingly, despite all these precautions, we have found an infection rate after prostatectomy of approximately 30%.

This paper reports two studies. In the first a comparison was made between the post-prostatectomy infection rate after saline or chlorhexidine bladder irrigation for the first 24 hours. In the second the infection rate after postoperative irrigation with chlorhexidine solution was compared with that after catheter drainage alone.

Patients and Methods

340 patients undergoing either retropubic or transurethral operations for benign or malignant prostatic obstruction were studied. Those infected before operation were excluded. Postoperative catheter drainage was through a 3-way 22 Ch Foley catheter and, where an irrigant was used, it was run in continuously through the side arm for 24 hours postoperatively.

Quantitative bacterial counts were made daily, by a tube dilution technique, while the patient was in hospital and at out-patient attendance 6 weeks later, using early morning mid-stream urine samples or samples obtained by needle puncture of the latex catheter.

Patients were considered to be infected if two consecutive samples contained more than 10^5 organisms per cm^3, or if the single sample at out-patients contained this number of organisms. Frequently, bacteriuria was noted in an isolated instance, subsequent samples being clear. In such patients infection was considered to be doubtful.

(i) Comparison of Postoperative Irrigation with Chlorhexidine or Saline Solutions

117 patients (108 with benign prostatic hypertrophy (BPH), and 9 with carcinoma of the prostate) were randomly allocated to 1 of 2 groups:

Group 1 (71 patients) received postoperative irrigation with chlorhexidine 1/5,000 in water.

Group 2 (46 patients) were irrigated with normal saline.

The groups were comparable with regard to age, history of previous infection, and the incidence of preoperative catheterisation for acute retention.

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Results

The trial was stopped when it became evident that the infection rate after chlorhexidine irrigation was significantly lower than that after saline (Table I). This difference in infection rates was significant when cases with BPH only were considered separately, as well as when all cases were considered together.

At the time this study was stopped there was a tendency for older patients to be infected more frequently than younger and for those with prolonged periods of catheter drainage to be infected more frequently than those with short. The differences were not significant. Breaking the catheter line to wash out clots had no detectable effect on the infection rate in this series.

Patients admitted with retention of urine and having a period of catheterisation preoperatively were not infected more frequently than elective cases provided the irrigant was chlorhexidine (Table II). If the irrigant was saline, preoperative catheterisation did appear to be associated with an increased risk of infection (Table III), though the trend was not significant.

(ii) Comparison of Infection Rates after Chlorhexidine Irrigation and after Drainage Alone

In this study 223 patients undergoing prostatectomy (201 with BPH; 21 with carcinoma of prostate), suitable for urethral catheter drainage, were randomly allocated to two groups:

In *Group 1* (107 patients) irrigation was not used, *i.e.* drainage alone group.

Group 2 (116 patients) were irrigated for 24 hours postoperatively with 1/5,000 chlorhexidine solution, *i.e.* irrigation group.

The groups were similar with regard to age, the incidence of elective operations, and the proportion of patients circumcised. There were fewer TUR's in the drainage alone group. The closed system of bladder drainage had to be broken more frequently (19 of 107 or 18%) in the drainage alone group than in the irrigation group (12 of 116 or 10·3%).

Table I

Infection Rate

	Chlorhexidine	Saline
Clear	36	14
Doubtful	13	9
Infected	22 (31%)	23 (50%)

χ_2 (doubtful with infected) = 3·84 $P<0{\cdot}05$
(doubtful with clear) = 3·50 $P\simeq0{\cdot}05$.

Table II

Ward or Theatre Catheterisation
(Saline Irrigation)

	Ward	Operating theatre
Clear	3	11
Doubtful	6	3
Infected	13 (61%)	10 (42%)
	—	—
	22	24
	Not significant	

Table III

Ward or Theatre Catheterisation
(Chlorhexidine Irrigation)

	Ward	Operating theatre
Clear	13	23
Doubtful	3	10
Infected	9 (36%)	13 (28%)
	—	—
	25	46

Results

Infection rate was similar in the two groups (Table IV). The similarity remains when cases of BPH or carcinoma of the prostate are considered separately, as well as for the whole group. But within these overall figures several trends can be identified:

Infection and the Type of Operation

Transurethural prostatectomy was followed by infection less frequently than retropubic operations. The difference was significant for the whole group (P= <0·025), but was particularly obvious in cases operated on for BPH (Table V).

The Effect of Age on the Infection Rate

Older patients were infected more frequently than younger ones. The infection rate for 113 patients under 70 years of age was 18% and for 100 patients of 70 years or more, 38%. This difference was highly significant (P= <0·005).

Infections and Complications of Catheter Drainage

Irrigation by syringe for clots and breaking the closed system in other ways were associated with a tendency to greater infection, which was not statistically significant (11/32 infected if the catheter line was broken, as compared to 48/190).

Circumcision and Infection

Circumcision might have been expected to be associated with a lower incidence of bacteriuria, but this was not so. The infection rate was 26·6% in the 124 uncircumcised men and 31·7% in the 63 circumcised.

Acute vs. *Elective Operations and Infection*

Acute cases admitted with retention of urine and catheterised in the ward prior to prostatectomy were infected more frequently (33·3%) than elective cases (21·8%). This difference was significant in those patients treated with drainage alone (P= <0·05). The infection rate in 54 cases admitted with retention and irrigated postoperatively with chlorhexidine was 28%, almost the same as that for the 62 irrigation cases having elective operations (24%). Irrigation thus appeared to reduce the incidence of infection in cases catheterised preoperatively.

The period of preoperative catheterisation did not appear to be related to the incidence of postoperative infection (cases infected preoperatively being excluded). In the groups treated with drainage alone the incidence of infection was 41% in the cases catheterised within 4 days of surgery, and exactly the same in the cases catheterised 5 or more days before. In the irrigation group the comparable figures were 29% and 26%.

Duration of Postoperative Catheterisation and Infection Rate

The chances of infection were greater if the catheter stayed in more than 4 days (46·7%) than if it was removed within 4 days (17·8%) and this difference was statistically highly significant (P= <0·001). The difference was similar in groups treated by drainage alone or irrigation.

If the catheter was removed within 3 days the infection rate was (15·7%). There was very little difference between the infection rates if the catheter was removed on the 4th postoperative day or on days 1 to 3, but if the catheter stayed more than 4 days the infection rate became significantly higher (P = <0·001).

Table IV

Infection Rate

	Drainage alone	Irrigation
Clear	59	63
Doubtful	18	23
Infected	30 (28%)	30 (26%)
	107	116

Table V

Infection Rate after Prostatectomy for BPH

	Retropubic *vs.*	Transurethral
Clear	64	47
Doubtful	27	11
Infected	40 (30·5%)	12 (17·1%)
	131	70

P (doubtful with infected) = 0·02–0·01.

Discussion

If continuous irrigation of the bladder is to be used at all after prostatectomy, the irrigation solution should contain an antiseptic. Irrigation with chlorhexidine 1/5,000 reduced the need to break the line to wash out clots, but it had no effect on the post-prostatectomy infection rate which was almost identical to that in patients treated by straight catheter drainage. However, the infection rate after saline irrigation was significnatly greater than that after chlorhexidine.

The infection rate was higher in elderly men and higher after retropubic operations than after TUR. Although patients admitted with acute retention and catheterised in the ward had a higher postoperative infection rate, the length of time the patient was catheterised preoperatively did not affect the outcome. Patients developing bacteriuria preoperatively were excluded from further study, but in those who did not the infection rate was approximately the same after 5 days or more as after 4 days or less of preliminary catheterisation. Ward catheterisation increased the risk of postoperative infection from 22 to 33% and for this group of patients irrigation with chlorhexidine did appear to confer a significant benefit, reducing the infection rate from 40% (of ward catheterised patients treated with drainage alone) to 28%. In fact the increase in infection associated with acute retention was largely due to the increase in cases treated by drainage alone postoperatively. This suggests that chlorhexidine irrigation has a place in the postoperative care of patients admitted with acute retention of urine.

There was no significant increase in infection rate if the catheter was kept for 4 days postoperatively (13%), as compared with 3 days or less (15%). But longer periods are followed by more frequent infections (54%. $P = < 0{\cdot}001$).

The interpretation of bacteriological results has been complicated by a number of instances in which bacteria were recovered in an isolated sample, previous and subsequent samples being uninfected. These "doubtful" samples were almost always MSU's, only 3 out of 40 occurring while the catheter was *in situ*. On 26 of the 40 occasions the doubtful sample was taken within 72 hours after the catheter had been withdrawn. It is possible that these samples were contaminated by passage through the urethra.

The reported incidence of urinary infection after urological operations has varied widely but rates as low as 6% have been reported in endoscopic prostatectomy (Webb and Blandy, 1968; Symes *et al.*, 1972). Our infection rate is much higher than this at approximately 28%.

A higher mortality and morbidity has previously been noted in non-teaching as opposed to teaching hospitals. This may be influenced by the older average age-group and the greater incidence of acute admissions in the peripheral hospitals. The combined effect of the factors influencing infection rate is important. Good risk cases in our series (men under 70 having a TUR as an elective procedure) had an infection rate of 7·1%. Bad risk cases (70 years plus, admitted with retention and having a retropubic operation) were more frequently infected (41%). It is clear that comparison between different series of cases cannot be made satisfactorily unless these factors are taken into account.

Summary

The incidence of post-prostatectomy bacteriuria was measured in patients having no continuous bladder irrigation postoperatively, in those irrigated for 24 hours with chlorhexidine 1/5,000, and in those irrigated with normal saline.

The infection rate after saline irrigation was greater than after chlorhexidine, but the infection rates after chlorhexidine irrigation and drainage alone were similar. The infection rate was higher in older patients, in those treated with retropubic rather than transurethral prostatectomies, in those who had postoperative catheters for more than 4 days, and in those admitted in acute retention of urine. The increase in infection rate associated with acute retention was seen only in the group treated with drainage alone postoperatively.

Chlorhexidine irrigation appears to reduce the infection rate in these cases.

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The Authors

J. R. G. Bastable, MS, FRCS, Consultant in Urology.
R. N. Peel, MRCPath, Consultant Microbiologist
D. M. Birch, SRN, Research Assistant.
B. Richards, MD, FRCS, Consultant in Urology.

Requests for reprints to Mr J. R. G. Bastable.

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The Effect of Antiandrogens and Stilboestrol on the Cytosol Receptor in Rat Prostate

R. GHANADIAN, C. B. SMITH, G. WILLIAMS and G. D. CHISHOLM
Prostate Research Laboratory, Royal Postgraduate Medical School, London, W12 0HS

It has been demonstrated that antiandrogens can act by inhibiting the binding of androgens within the prostatic cell in both experimental animals and man (Fang and Liao, 1969; Dorfman, 1971; Hansson and Tveter, 1971; Sufrin and Coffey, 1973). Some of these compounds have been used in the management of patients with prostatic tumours and these reports have provided considerable information regarding their various actions (Scott and Wade, 1969; Chisholm and O'Donoghue, 1975; Jonsson and Nilsson, 1976). However, there is no reliable index or method for choosing a particular antiandrogen for clinical practice due to the fact that in most of these investigations the drugs have not been compared in an equimolar system. In addition, little is known about the effects of stilboestrol, the most widely used oestrogen, on the steroid receptor complex in the prostate.

In the present study we have measured equimolar effects of representative compounds from 3 main classes of antiandrogens and the non-steroidal oestrogen, stilboestrol, on the dihydrotestosterone receptor complex isolated from rat prostate. These effects have been compared to the inhibitory effect of a similar concentration of testosterone.

Materials and Methods

Animals. Male albino Wistar rats of 300 to 400 g body weight were used in all experiments. Bilateral orchidectomy was performed, under fluothane anaesthesia, 24 hours prior to the experiment.

Steroids. $[1\alpha,2\alpha\text{-}^{3}\mathrm{H}]$ testosterone, Sp. activity, 49 Ci/mmol (Radiochemical Centre, Amersham, UK). The following unlabelled steroids were used: testosterone, 5α-dihydrotestosterone, androsterone (3α-hydroxy-5α-androstan-17-one), androstanediol (5α-androstane-3β,17β-diol), androstenediol (androst-5-ene-3β,17β-diol), androstanedione (5α-androstane-3,17-dione) and androstenedione (androst-4-ene-3,17-dione).

Antiandrogens. 3 classes of antiandrogens were used:
(a) *17α-hydroxyprogesterone derivatives:* Cyproterone acetate (Schering) and chlormadinone acetate (Syntex).
(b) *19 nor-testosterone derivative:* 17α-(2-methallyl) 19 nortestosterone (SC 9022) (Searle).
(c) *Non-steroidal antiandrogen:* Flutamide (SCH 13521, Schering, USA).

Other Compounds. Diethylstilboestrol.

Solvents. Redistilled chloroform, acetone, diethyl ether (peroxide free), Triton X-100 and Toluene (Analar grade).

Chromatographic Materials. Sephadex G-25 and G-200. Aluminium-backed silica gel plates, F254 for thin layer chromatography (T.L.C.).

Scintillation Fluid. Toluene: Triton X-100 (2 : 1) containing 0·4% diphenyloxazole (P.P.O.) was used for aqueous samples. Toluene containing 0·4% (w/v) P.P.O. was used for all other samples.

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

Buffers. Two buffers were used. Buffer A: 20 mM Tris-HCl buffer, pH 7·4 containing 320 mM sucrose and 3 mM magnesium chloride. Buffer B: 20 mM Tris-HCl buffer, pH 7·4 containing 1·5 mM EDTA, disodium salt and 2 mM 2-mercaptoethanol.

Preparation and Labelling of Tissue

Prostatic tissues were labelled either *in vivo* or *in vitro* and subsequently subjected to cell fractionation.

(*a*) In vivo *Experiments*

Animals castrated 24 hours previously received an intraperitoneal injection of 1 μM/100 g body weight of the test drug in ethanol/saline (1 : 1 v/v). Control animals received an equal volume of ethanol/saline only. Each animal received 10 μCi/100 g body weight $[^{3}\text{H}]$ testosterone in 20% ethanol/saline following the injection of drug. 1 hour after the administration of radioactivity the animals were killed and for each experiment the prostates from 2 animals were pooled. The tissue was minced, blotted, weighed and used for cytosol preparation.

(*b*) In vitro *Experiments*

24-hour castrated rats were sacrificed and the ventral prostates dissected out. For each experiment prostatic tissue was pooled from 3 animals. The tissue was minced and washed 3 times in buffer A prior to incubation with 0·25 μCi of $[^{3}\text{H}]$ testosterone per 2 ml of buffer A with or without tested drug at 0·1 μM. The tissue was incubated at 30°C

Table I

Comparison of the Effect of Antiandrogens and Testosterone on the *in vitro* uptake of $[^{3}\text{H}]$ Testosterone by Rat Ventral Prostate. Values are Mean ± S.E.M.

Compound (Number of experiments)	Uptake of $[^{3}\text{H}]$ testosterone	dpm/mg Tissue	% Inhibition
	Control	*With compound*	
Testosterone (10)	1807·2±116·2	834·3±131·4	53·3±6·9
Cyproterone acetate (7)	1781·9±138·3	1015·8±102 7	42·5±4·2
Chlormadinone acetate (7)	1595·6±152·7	994·2±68·7	36·3±4·2
SC 9022 (13)	1850·0±115 0	991·8±82·5	46·2±2·7
Flutamide (22)	1305·5±61·5	1319·5±67·0	No inhibition

Table II

In vivo and *in vitro* Metabolites of $[^{3}\text{H}]$ Testosterone, recovered from the Steroid Receptor Complex, isolated from the Cytosol of Rat Ventral Prostate

	% Steroid recovered (mean ± S.E.M.)	
Steroids recovered	*In vivo*	*In vitro*
Dihydrotestosterone	79·07±2·52	77·40±4·74
Testosterone	10·67±1·64	7 46±1·71
Androstanediol Androstenediol	2·87±1·07	6·92±1·65
Androstendione	2·97±0·35	3·02±0·58
Androsterone	1·47±1·32	0·58±0·25
Androstanedione	<0·57	2·80±0·64
Others	2·43±0·26	1·82±0 45

for 1 hour and subsequently was washed 3 times with buffer A, blotted, weighed and used for the preparation of cytosol.

Uptake Studies

In vitro uptake of radioactivity by prostatic tissue was carried out as described previously (Ghanadian and Fotherby, 1970). The incubation media contained 100 μg of test drug and 0·25 μCi of [^{3}H] testosterone per 2 ml media.

Preparation of Cytosol

Labelled tissue from *in vivo* or *in vitro* experiments was homogenised with a Teflon-glass motor-driven homogeniser in 3 volumes of buffer B using 5 strokes each of 10 sec duration and 30 sec cooling intervals. The homogenate was centrifuged at 105,000 g for 1 hour at 2°C. The cytosol was removed. Aliquots (0·05 ml) were taken for the measurement of protein and the remainder stored at −20°C for analysis.

Analysis of the Cytoplasmic Extract

(*a*) Characterisation of the receptor protein was performed by sucrose gradient centrifugation (Ghanadian, Smith and Chisholm, 1977).

(*b*) Binding analysis. Cytoplasmic extracts (1·0 ml) were subjected to gel-filtration on either Sephadex G-200 or G-25 columns, eluted with buffer B at a flow-rate of 50 cm^3/hour and fractions of 2 ml were collected. Aliquots (1 ml) from each fraction were transferred to scintillation vials together with 10 ml of scintillation fluid and the radioactivity was counted in an Intertechnique SL40 scintillation spectrometer.

Analysis of Radiometabolites

Radiometabolites were identified as previously described (Ghanadian, Smith and Chisholm, 1977).

Other Procedures

Protein was measured in 0·05 ml aliquots of cytosol using bovine serum albumin as described by Lowry *et al.* (1951).

Results

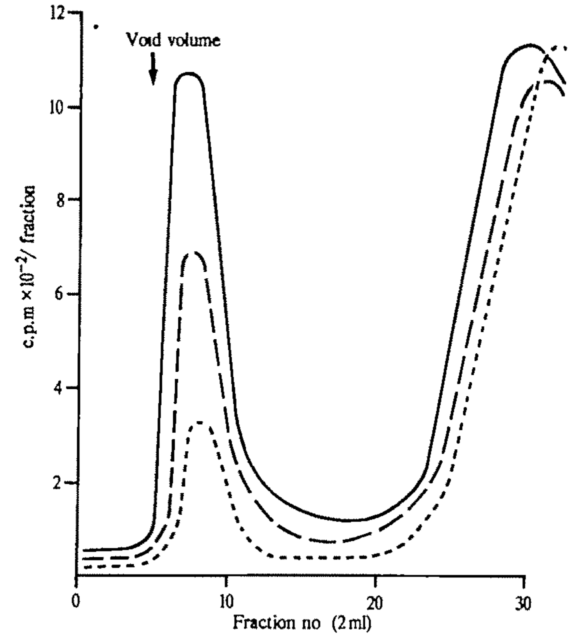
1. *Uptake Studies*

The *in vitro* effects of antiandrogens on the uptake of tritiated testosterone by the whole tissue are shown in Table I. In this study, no effect was observed with flutamide while the remaining 3 antiandrogens produced similar inhibitory effects on the uptake of tritiated testosterone.

Table III

In vivo and *in vitro* Inhibition of [^{3}H] Dihydrotestosterone binding to the Cytoplasmic Receptor Proteins from the Rat Ventral Prostate by Testosterone and Antiandrogens

Compound (Number of experiments)	% Inhibition			
	In vivo		*In vitro*	
	Mean ± S.E.M.	Range	Mean ± S.E.M.	Range
Testosterone (5)	89·55 ± 2·60	81·94-93·74	76·88 ± 2·68	67·82-83·26
Cyproterone acetate (5)	49·46 ± 3·94	40·21-60·59	47·01 ± 2·47	40·75-55·16
Chlormadinone acetate (5)	50·89 ± 8·28	20·10-66·70	48·55 ± 1·77	43·92-54·89
SC 9022 (5)	56·68 ± 5·69	36·35-67·96	44·33 ± 5·45	24·62-55·68
Flutamide (5)	44·39 ± 5 25	25·95-51·24	No inhibition	–
Stilboestrol (5)	No inhibition	–	2·46 ± 1·62	0-8·0



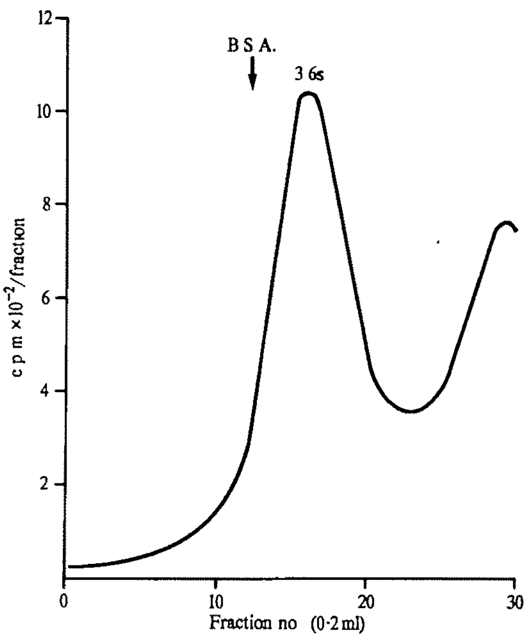


Fig. 1. A typical example of the inhibition of $[^3H]$ dihydrotestosterone binding to the receptor complex by tested compounds. The samples were analysed on Sephadex G-25. Radioactivity elution profiles of the cytosol are shown for (*a*) untreated (————), (*b*) cyproterone acetate (0·1 μM) (— — —), (*c*) testosterone (0 1 μM) (- - - -).

Fig. 2. Analysis of prostatic cytosol on sucrose density gradients in the presence of 0 4 M KCl. Labelled cytosol from 24-hour castrated rats was centrifuged at 60,000 rpm for 16 hours at 2°C. Sedimentation was from right to left. Bovine serum albumin with a sedimentation coefficient of 4·6 sec was used as a standard.

2. *Separation of the Receptor and Identification of Radiometabolites*

The steroid receptor complex was isolated by column chromatography. The binding patterns on Sephadex G-25 (Fig. 1) and G-200 were found to be similar. This binding protein was then analysed by gradient centrifugation. When high salt solution (0·4 M KCl) was used the sedimentation coefficient was found to be 3·6 sec (Fig. 2). Analysis of $[^3H]$ steroids associated with the binding protein was carried out by thin layer chromatography. In both *in vivo* and *in vitro* studies 77 to 79% of the radioactive steroid recovered was 5α-dihydrotestosterone. Testosterone was only 7 to 10% of the radioactivity recovered. Other androgens were present at a much lower level (Table II).

3. *Effects of Test Compounds on the Cytoplasmic DHT Receptor*

For the routine measurement of the effect of antiandrogens and stilboestrol on the binding of dihydrotestosterone to the receptor complex, samples were sequentially analysed on a column of Sephadex G-25 (Fig. 1). The total counts associated with bound radioactivity (fractions 5 to 10) were adjusted for variations in the protein content of the applied cytosol and the percentage inhibition compared to the control (untreated) was calculated.

The inhibitory effect of 1 μmol/100 g body weight of the 4 test antiandrogens on the dihydrotesterone receptor complex *in vivo* ranged from 44·39 to 56·6%. Apart from the 19-nor-testosterone derivative (SC 9022) which produced a somewhat higher inhibition than the non-steroidal compound (flutamide) no other significant differences were observed. The two 17α-hydroxyprogesterone derivatives tested in this experiment (cyproterone acetate and chlormadinone acetate) produced an almost identical effect on the cytosol receptor protein both *in vivo* and *in* *vitro*. Flutamide produced no *in vitro* effect. The non-steroidal oestrogen (stilboestrol) had negligible *in vitro* and no *in vivo* effect on the cytoplasmic DHT receptor complex (Table III).

Discussion

When the inhibitory effects of equimolar doses of antiandrogens and stilboestrol were compared to that of testosterone, a significantly higher inhibition was produced by testosterone. This applied to both *in vivo* and *in vitro* experiments. There was no significant difference between the *in vivo* inhibitory effects amongst the 3 classes of antiandrogens tested. Stilboestrol did not produce any *in vivo* effect. With the exception of flutamide, similar results were observed *in vitro*. Previous studies have demonstrated the equipotency of cyproterone acetate and flutamide, *in vivo* (Neri *et al.*, 1972; Liao, Howell and Chang, 1974).

In the present study, the potency of 17α-hydroxyprogesterone derivatives (cyproterone acetate and chlormadinone acetate) and the non-steroidal compound (flutamide) was found to be similar *in vivo*. However, no *in vitro* effect was observed with flutamide. Katchen and Buxbaum (1975) found that following the injection of tritiated flutamide in man more than 97% of the compound was converted to several radiometabolites. They suggested that the side-chain hydroxylated metabolite could be the active form of this compound. This may explain the inability of flutamide to act *in vitro*.

Our results also suggest that the 19-nor-testosterone derivative (SC 9022) is somewhat more active than flutamide. Skinner *et al.* (1975) found that 19-nor-dihydrotestosterone derivatives were slightly more potent than cyproterone acetate. It appears that the addition of a methylene group to 17α-hydroxyprogesterone derivatives does not alter the potency of the compound and that cyproterone acetate produces similar effects to chlormadinone acetate.

Stilboestrol was included in this study because of its wide use in patients with prostatic carcinoma. We did not consider stilboestrol an antiandrogen in the strict sense since this drug does not compete with testosterone at the target tissue level (Dorfman, 1971). This study clearly demonstrates that stilboestrol does not have an inhibitory effect on the cytoplasmic binding of 5α-DHT to the receptor. Fang, Anderson and Liao (1969) reported only slight effect of stilboestrol on the nuclear retention of 5α-dihydrotestosterone using 500 times higher concentration than used in this study. It has been well documented that stilboestrol substantially reduces the level of plasma testosterone by inhibiting gonadotrophin production as well as stimulating sex hormone binding globulin (SHBG) in man (Jonsson and Nilsson, 1976). Some effect of stilboestrol on the 5α reductase has also been reported. In an *in vitro* study, Lee *et al.* (1973) measured the inhibitory effects of 6 oestrogens on the testosterone reduction in rat prostate and found that only those oestrogens with a complete steroid structure and a free phenolic hydroxyl group at position 3 of the steroid nucleus inhibited testosterone 5α reduction. However, in liver this structural requirement was not essential. They concluded that there was a negligible effect of stilboestrol on the conversion of testosterone to 5α-dihydrotestosterone in the prostate. Similarly, Belham and Neal (1971) found little effect on this enzyme in rat prostate. Other research groups (Farnsworth, 1969) have reported more effect of stilboestrol on this enzyme in the prostate.

In the present study the existence of a receptor protein which binds preferentially to dihydrotestosterone was confirmed. In the presence of a high salt solution the steroid receptor complex had a sedimentation coefficient of 3·6 sec and this is in agreement with previous reports characterising receptor proteins (Ghanadian, 1976). Analysis of the [^{3}H] steroids associated with the receptor complex showed that 77 to 79% of the radioactivity recovered was dihydrotestosterone. Other workers have reported that 69% (Rennie and Bruchovsky, 1972) and 85% (Fang *et al.*, 1969) of the steroid bound to the receptor was dihydrotestosterone.

Summary

The effects of 4 antiandrogens and stilboestrol on the cytosol receptor of the rat ventral prostate have been compared.

Equimolar doses of cyproterone acetate, chlormadinone acetate, SC 9022 and flutamide inhibited the binding of dihydrotestosterone to the receptor complex *in vivo* by 44 to 50% whereas stilboestrol had no effect. In the *in vitro* studies an equimolar concentration produced similar effects to those observed *in vivo* with the exception of flutamide which had no effect.

This technique provides a method for assessing and comparing the effectiveness of antiandrogens on the androgen receptor complex of the prostate.

The authors wish to thank the Medical Research Council for financial support.

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The Authors

R. Ghanadian, PhD, Lecturer and Research Fellow.
C. B. Smith, MA(Cantab), Research Assistant.
G. Williams, FRCS, Senior Urological Registrar.
G. D. Chisholm, ChM, FRCS, Consultant Urological Surgeon and Senior Lecturer.

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Differential Androgen Uptake by the Lobes of the Rhesus Monkey Prostate

R. GHANADIAN, C. B. SMITH, G. D. CHISHOLM and *N. J. BLACKLOCK

*Prostate Research Laboratory, Urological Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London, and *Royal Naval Hospital, Haslar*

The prostate of the rhesus monkey (*Macacca mulatta*) lies on the dorsal aspect of the urethra and consists of 2 anatomically discrete lobes, a cranial and a caudal (Fig.). The surface of the cranial lobe is deeply furrowed, resembling that of the seminal vesicles whilst the caudal lobe is more closely applied to the urethra and has a smooth surface. The cranial lobe is easily separable from the seminal vesicles above and surrounds the terminal vas deferens and the duct of the seminal vesicles on each side as these pass downwards and forwards to the urethra. The cranial and caudal lobes are separate peripherally but antero-medially the 2 lobes merge where the ducts from the cranial lobes in company with the common ejaculatory ducts penetrate the flat surface of the caudal lobe before passing through the wall of the urethra at the level of the verumontanum.

This morphology in the monkey is directly comparable with the zonal anatomy of the functional human prostate as described by McNeal (1968), the cranial lobe equating with the central zone in the human and the caudal lobe with the peripheral zone. There are distinctive histological differences between the cranial and caudal lobes and these resemble the differential features of the human central and peripheral zones respectively (Blacklock and Bouskill, 1977). There are therefore grounds for considering that the comparable regions are homologous.

Study of the pathological and age-related changes in the functional prostate of the human have shown that the peripheral zone is more susceptible to inflammation, degeneration and neoplasia (McNeal, 1968) and that whilst the central zone acini appear to differentiate before puberty those of the peripheral zone develop either at puberty or thereafter. This differential acinar development suggests a greater dependence of the peripheral zone on an androgen stimulus (Blacklock, 1976). The differential susceptibility to disease may also have a hormonal basis.

In view of the morphological grounds for considering the cranial and caudal lobes of the monkey prostate to be homologous with the human central and peripheral zones respectively and with the ability to define and separate these 2 parts of the prostate of the monkey, this animal appeared particularly suitable for comparative studies of the 2 parts of the gland. In this instance, the differential ability of the 2 lobes to take up and retain androgens was investigated and also compared with other non-target tissues.

Materials and Methods

Animals: 10 rhesus monkeys aged 5-10 years were studied. Prostate and other tissues were removed while the animal was under general anaesthesia. The tissue was immediately transferred to a container, kept on ice and transported to the laboratory. The 2 lobes of the prostate were clearly dissected from adjacent connective tissue. Slices of approximately 20-30 mg tissue were transferred to incubation flasks containing 0·25 μCi [^{3}H] testosterone (S.A. 49 Ci/mmol, Amersham, UK) in 2 ml buffer consisting of 20 mM tris HCl, 320 mM sucrose and 3 mM Mg Cl_2 pH 7·4. Incubation conditions and washing procedures were carried out as described previously (Ghanadian and Fotherby, 1970). When required a 100-fold or 1,000-fold excess unlabelled testosterone (Sigma

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Chemicals) was introduced in the media. The tissue was weighed and dissolved with 0·5 ml soluene 350 (Packard) in scintillation vials. Scintillation fluid (10 ml) consisted of 0·4% of 2,5-diphenyloxazole (PPO) (Koch-Light Laboratory) in Toluene AR (BDH) was added and the radioactivity was counted in a liquid scintillation spectrometer (SL 40 Intertechnique). Quench correction was carried out using internal standard method. The results were expressed in disintegrations per minute (d/min)/mg wet tissue.

Results

The uptake of [^{3}H] testosterone by the caudal and cranial lobes of the prostate was measured and the results were compared with those of the seminal vesicles, urethra, muscle and liver (Table I). Statistical analysis of the results (*t* test) showed significantly higher uptake by the caudal lobe of prostate ($P < 0·001$) when compared with any other target or non-target tissues tested. The uptake by the cranial lobe was significantly higher than the muscle or urethra ($P < 0·001$) but not seminal vesicle ($P > 0·1$). The uptake by the liver varied considerably due to the high degree of blood contamination.

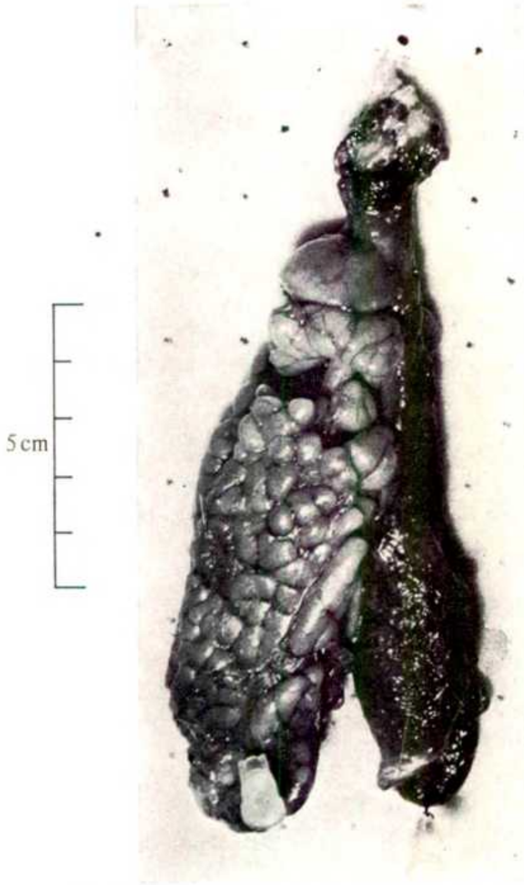

Fig. Lateral view of the lobes of the rhesus monkey prostate which lie on the posterior aspect of the urethra. The 2 lobes are easily separable peripherally and the duct of the seminal vesicle with the vas deferens can be seen to pass into the upper aspect of the cranial lobe.

Table I

In vitro Uptake of [^{3}H] Testosterone by Various Tissues of the Rhesus Monkey

	Caudal	Cranial	Muscle	Liver	Seminal vesicle	Urethra
Mean ± S.E.M. (d/min/mg tissue)	482·1 ± 16·3	284·7 ± 17·2	188·4 ± 10·2	347·3 ± 28·7	332·0 ± 18·1	176·1 ± 16·9
No. of animals	10	10	10	10	4	3
No. of samples	31	31	31	31	14	10

d/min = disintegrations per minute.

Table II

The Effect of Simultaneous Incubation with a 100-fold excess of Unlabelled Testosterone on the *in vitro* Uptake of [^{3}H] Testosterone

	Uptake of [^{3}H] testosterone			
	Without unlabelled testosterone	With unlabelled testosterone	Significance (value for P)	Decrease %
Caudal	431·2 ± 23·7	325·9 ± 20·8	< 0·01	24·4
Cranial	255·8 ± 29·3	196·0 ± 23·7	< 0·05	23·4
Muscle	139·2 ± 9·8	129·6 ± 8·9	NS	6·9
Liver	429·6 ± 56·2	553·9 ± 79·4	NS	–

Values are expressed in d/min/mg of tissue wet weight. Values were the mean from 6 animals, each tissue was estimated in duplicate. Unlabelled testosterone was included in the media at a concentration of 74 ng/ml. The concentration of [^{3}H] testosterone was 0·125 μCi/ml (0·74 ng/ml). For the effect of 1,000-fold excess see text.

The inclusion of a 100-fold excess of unlabelled testosterone in the media produced a significant decrease in the uptake of [^{3}H] testosterone by prostatic tissues. At this concentration the uptake by the prostatic tissue was inhibited approximately 24%. The results are shown in Table II. However, when a 1,000-fold excess of testosterone was introduced to the incubation media the inhibition by the caudal lobe was increased to 46%, whereas no further reduction was observed in the cranial lobe.

Discussion

The results demonstrate a significantly higher uptake of [^{3}H] testosterone by the caudal lobe of the prostate than any of the other tissues examined. In previous reports using rat prostate (Tveter, 1969; Ghanadian and Fotherby, 1970) and human prostate (Hansson *et al.*, 1971; Ghanadian, 1976) it has been shown that prostatic tissue takes up and retains androgens more than non-target tissues. Furthermore, a differential uptake of androgens has been demonstrated in the various lobes of the rat prostate (Tveter, 1969).

In the present study there is a distinct difference in the ability of the caudal and cranial lobes to take up androgen. The uptake of [^{3}H] testosterone and the inhibitory effect of unlabelled testosterone is profoundly greater in the caudal lobe suggesting that this part of the gland is more sensitive to androgen. This may be due to a higher level of androgenic receptor in this lobe. The finding is of interest in consideration of the observation that the acinar development of the homologous region in the human gland, the peripheral zone, appears to be delayed until puberty (Blacklock, 1976). In contrast, the cranial lobe has a lesser uptake of androgen and in this respect behaves in the same manner as seminal vesicular tissue.

Further studies are required to confirm the differential receptor population in the 2 lobes of the monkey prostate.

Summary

The prostate of the rhesus monkey (*Mucacca mulatta*) consists of a cranial and a caudal lobe.

The uptake of [^{3}H] testosterone by these 2 lobes has been measured and compared with control tissues. A significantly higher uptake of radioactivity was found in the caudal lobe when compared to cranial as well as other control tissues. The uptake of radioactivity by the caudal and cranial lobes was suppressed when unlabelled testosterone was introduced into the incubation media.

The relationship between these 2 lobes of the monkey prostate and the central and peripheral zones of the human prostate is described.

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The Authors

R. Ghanadian, PhD, Lecturer and Research Fellow.
C. B. Smith, MA, (Cantab) Research Assistant.
G. D. Chisholm, ChM, FRCS, Consultant Urological Surgeon and Senior Lecturer.
N. J. Blacklock, OBE, FRCS, Surgeon Captain, R.N., Consultant Urologist.

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Early Diagnosis of Prostatic Carcinoma: The Role of Transurethral Resection

E. P. N. O'DONOGHUE and R. C. B. PUGH
Institute of Urology and St Paul's Hospital, London

The use of transurethral resection (TUR) in prostatic surgery has created problems for the histopathologist as discussed by one of us (R. C. B. P.) in a Presidential Address to the Section of Urology at the Royal Society of Medicine. The main function of the histopathologist in this setting is to confirm the diagnosis of carcinoma when it is suspected on clinical grounds or to exclude it in the clinically benign gland. In contrast to open prostatectomy specimens, correct anatomical orientation of TUR material is not usually possible. In routine practice the histopathologist can sample only a proportion of the tissue received because examination of all resected tissue is impracticable, especially if the excised gland is large. The diagnosis of carcinoma from TUR specimens is therefore to some extent a lottery subject to sampling errors at surgery if resection has been incomplete, and again at histological examination. An attempt has been made to resolve these difficulties by separation of tissue on an anatomical basis during resection and the submission of 3 specimens for histopathological examination.

The primary objective was to assess the feasibility of an anatomical separation of tissue and thus more representative histological sampling of TUR specimens. The secondary objectives were to use this technique to characterise prostatic carcinoma more accurately in terms of size and extent of the primary tumour and to attempt to increase the detection rate of early disease.

Patients and Methods

The study was carried out on 50 men undergoing elective transurethral prostatectomy for bladder outlet obstruction. The mean age was 66·4 ± 8 years (range 44 to 88 years). Men with clinically apparent prostatic carcinoma underwent prostatic resection only when there was evidence of bladder outlet obstruction as shown by residual urine volumes or conventional urodynamic studies.

During TUR the tissue was subdivided into 3 parts, 1 from each lateral area and 1 from the posterior area (Fig. 1). Particular attention was paid to resection of the posterior portion in the expectation that this would provide the most likely source of carcinoma. The technique of Barnes (1943) has been used, resecting first the lateral tissue on either side after definition of the bladder neck fibres posteriorally and then the posterior portion with careful evacuation of tissue on completion of each stage. This triple specimen technique does not add significantly to the operating time.

Results

The mean weight of tissue at each resection was 25·5 g with a range of 8 to 95 g. The mean weights for each lateral specimen were 10 g and 10·2 g and for the posterior specimen 5·4 g (Table I).

Carcinoma was the preoperative clinical diagnosis in 10 patients (Table II). 3 of these were found to have benign disease on histological examination after TUR and follow-up transrectal needle biopsy. The 7 clinically neoplastic cases all had extensive disease with involvement of the

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posterior specimen and one or both lateral specimens in 6 and diffuse involvement of the posterior specimen only in 1. 4 of the 7 had metastases in bone and 1 had histologically proven lymph node metastases. In 2 the lymph nodes were not assessed.

In only 1 of the 40 patients with a clinical diagnosis of benign disease was carcinoma found on histological examination after TUR. Again there was extensive involvement of all 3 specimens but skeletal studies were negative and the nodes were not assessed.

Discussion

The principal finding of this pilot study is that segregation and selection of tissue at TUR is of great help to the histopathologist. Firstly it ensures more representative sampling from all 3 areas. Secondly, if a small area of carcinoma is found on sampling the histopathologist can readily select more tissue from that specimen for further examination and assessment. The posterior specimen accounts for approximately one-fifth of the total and it is therefore entirely feasible to block it out completely for histological examination in the majority of cases.

The chief advantage of this policy is that the histopathologist can assess the extent of the tumour within the prostate. This is more precise than rectal examination in the differentiation of small lesions with a good prognosis from more extensive disease and this information can help greatly in management (O'Donoghue *et al.*, 1976).

Rather surprisingly, only 1 unsuspected carcinoma was found in 40 cases—a rate of 2·5%. Although this low detection rate may reflect a high clinical index of suspicion in a unit with a special interest in prostatic carcinoma, it seems more likely that even this triple sampling technique is insufficient for the detection of small tumours. The value of detecting small lesions may of course be questioned in view of their favourable natural history but their detection is at least a ready confirmation that histological sampling has been adequate. The reported incidence of prostatic carcinoma at post-mortem examination is in the range of 14 to 24% which greatly exceeds the clinical incidence of the disease (Table III). It is clear that many of these are of such a

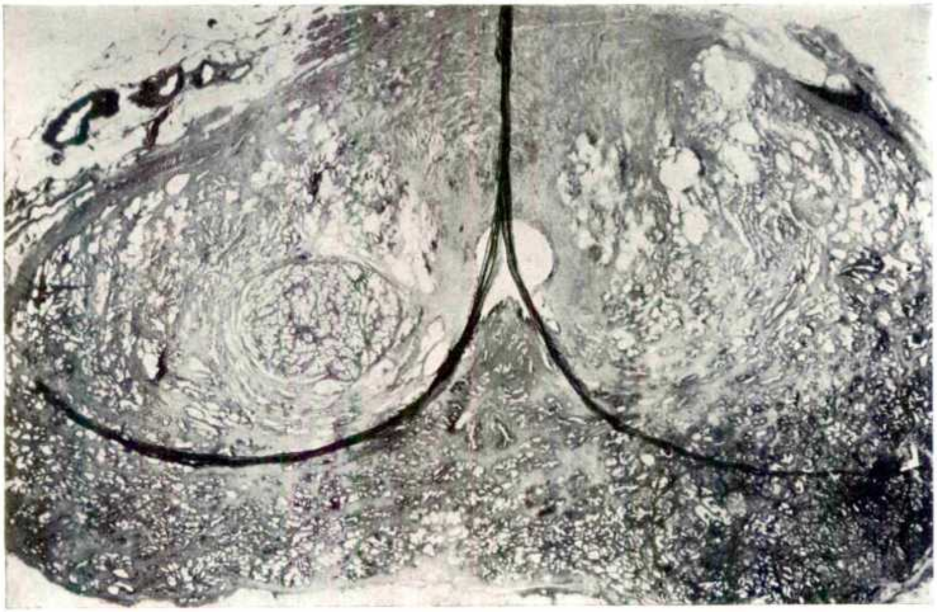

Fig. 1. Transverse section of prostate at proximal margin of veru montanum indicating subdivision of resected tissue into 3 separate specimens. A small area of carcinoma is present in the R postero-lateral area.

Table I

Weights of Triple Specimen Resections in 50 Patients

Weights (grams)	Total specimen	R lateral	L lateral	Posterior
Mean and S.D.	25·5 ± 18·2	10·0 ± 7·9	10·1 ± 7·4	5·4 ± 4·9
Range	8-95	3-43	3-37	0·1-22
Totals	1277	500	506	271

Table II

Preoperative Clinical Diagnosis, Distribution of Tumour and TNM Classification in 50 Patients

Clinical diagnosis	Histology					
			Lateral	*Posterior*		
10 Malignant	3B					
	7M	6	+	+	T3 (5)	M1 (3)
					T4 (1)	N+ (1)
		1	0	+	T3 NX M1	
40 Benign	39B					
	1M		+	+	T0 NX M0	

size that they can only be found by serial or step-section techniques which are impracticable as a routine procedure. The incidence of unsuspected lesions at prostatectomy in reported series is approximately half that of the post-mortem series (Table IV) and these rates are based largely on open prostatectomy. Denton, Choy and Valk (1965) reported a 6% rate with routine histological examination of TUR specimens and a 21% rate if step-section was used. Barnes and Ninan (1972) have shown that the detection rate of TUR can be increased by 20% if tissue from the posterior and apical areas is selected for histological examination. The work of McNeal (1969) and of Blacklock (1974) on the internal anatomy of the prostate is relevant and may provide the explanation of these discrepancies (Fig. 2). In the adolescent male the true prostate is composed largely of a cone-shaped central zone the long axis of which is formed by the ejaculatory ducts and a peripheral zone which lies both peripheral and caudal to the central zone like a funnel imposed on a cone. McNeal has shown that carcinoma arises predominantly in the peripheral zone. With ageing and the development of benign prostatic hyperplasia from periurethral glands the true prostate is compressed peripherally (Fig. 3). In this situation, our posterior specimen is derived principally from the central zone and our lateral specimens principally from benign hyperplastic tissue. Selection of tissue from the peripheral zone would seem to be essential to exclude the presence of carcinoma.

The 3-stage technique reported here is inadequate for the diagnosis of small lesions and perhaps should be replaced by a 4-stage procedure. It is suggested that one should first resect a cone-shaped area from bladder neck to veru and segregate this tissue into right and left lateral and posterior specimens (Fig. 4). The remaining tissue at the periphery and apex corresponds

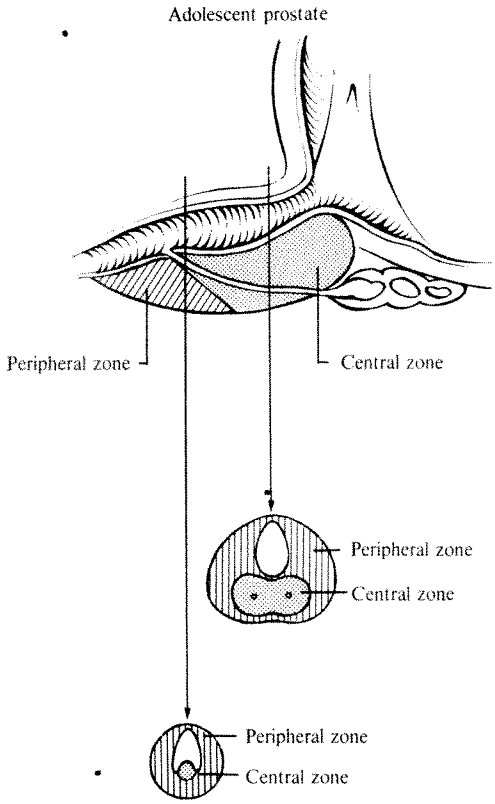

Fig. 2. Central and peripheral zones in adolescent prostate. Redrawn after McNeal.

anatomically to the peripheral zone and resembles chords of a circle in coronal section. Resection of this remaining tissue is the final step and should again be labelled and submitted separately for pathological examination.

Conclusions

1. Segregation of TUR material on an anatomical basis into 3 separate specimens is of considerable value to the histopathologist. It allows a more representative histological sampling of the prostate and a semiquantitative assessment of the extent of prostatic carcinoma.
2. It offers the urologist a more precise characterisation of prostatic carcinoma which may help to select those for more extensive staging investigation and to choose treatment modalities.

Table III

Incidence of Prostatic Carcinoma found at Post-mortem Examination in 4 Reported Series.

Moore (1935)	16·7%
Rich (1935)	14·0%
Kahler (1939)	17·3%
Emmett *et al.* (1962)	24·0%

Table IV

Incidence of Unsuspected Prostatic Carcinoma after Prostatectomy

Smith and Woodruff (1950)	9·0%
Bauer *et al.* (1959)	6·5%
Denton *et al.* (1965)	6·0%
	Step-section→21·0%
Varkarakis *et al.* (1970)	4·9%

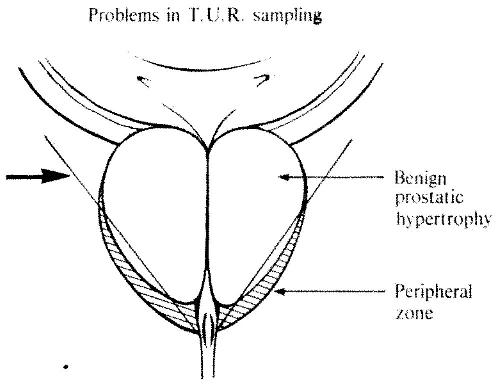

Fig. 3. Diagrammatic representation of changes within prostate with development of benign prostatic hyperplasia.

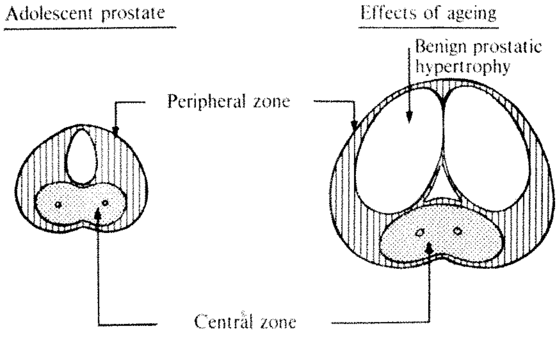

Fig. 4. Method of sampling peripheral zone during TUR.

3. It has not led to an increased detection rate of unsuspected tumours in this pilot study.
4. Separation of a fourth specimen from the peripheral zone is desirable.

Summary

The exclusion of prostatic carcinoma in TUR specimens represents a considerable problem for the histopathologist.

A technique for the separation of tissue on an anatomical basis which has been carried out on 50 patients is presented.

It permits more representative histological sampling of TUR specimens and more accurate characterisation of prostatic carcinoma, but further refinement is recommended.

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The Authors

E. P. N. O'Donoghue, FRCS, Senior Lecturer and Honorary Consultant, Institute of Urology.
R. C. B. Pugh, MD, FRCPath, Consultant Pathologist, St Paul's Hospital.

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Urine Hydroxyproline Excretion—a Marker of Bone Metastases in Prostatic Carcinoma

M. C. BISHOP and G. J. FELLOWS
Nuffield Department of Surgery and Urology, Radcliffe Infirmary, Oxford

Urinary excretion of the imino acid hydroxyproline, one of the constituentsof the polypeptide chains in collagen, is a reliable marker of bone matrix turnover (Prockop and Kivirikko, 1967). An increased daily output, mainly in peptide form, is found in a variety of conditions in which rates of bone formation or resorption are excessive. Examples include benign disorders such as Paget's disease, hyperparathyroid bone disease and thyrotoxicosis, and malignant disease with skeletal deposits (Platt, Doolittle and Hartshorn, 1964; Bonadonna *et al.*, 1966; Hosley *et al.*, 1966). In breast carcinoma the total urinary hydroxyproline may be a more sensitive indicator of bone metastases than X-rays or isotope scanning (Cuschieri, 1973; Sumner *et al.*, 1973; Powles, Leese and Bondy, 1975).

With renewed interest in radical treatment of prostatic carcinoma, accurate staging of the disease at presentation has assumed greater importance. Moreover, critical assessment of the effects of various forms of hormone and cytotoxic drug therapy requires an adequate marker of activity of metastases. The recognition of deposits in bone has hitherto been based on skeletal radiology, plasma levels of calcium and alkaline phosphatase, serum and bone marrow acid phosphatase and more recently bone biopsy and scintiscanning. All these have disadvantages. In the present study, urinary hydroxyproline is evaluated as a biochemical marker of the presence and progress of bone metastases in patients with prostatic carcinoma.

Patients and Methods

35 patients (aged 48-83) with histologically proven carcinoma of the prostate were studied. They all had normal renal function (plasma creatinine less than 140 μmol/l). Skeletal metastases were diagnosed from bone scans (^{99m}Tc MDP Radiochemical, Amersham—Subramanian *et al.*, 1975) and radiologic skeletal surveys. Hormone treatment was given as stillboestrol except for 1 patient who was studied after orchidectomy and another on treatment with cyproterone acetate. In both of these cases local disease had progressed despite previous treatment with conventional oestrogens. In 2 patients, radiotherapy was given to painful local deposits. Patients were asked to take a diet low in collagen-containing products for 48 hours and to collect urine for the whole of the second 24-hour period. The volumes of refrigerated specimens were measured and aliquots retained for hydroxyproline, calcium and creatinine determination. Blood was taken for serum acid phosphatase (formol-stable fraction) and plasma alkaline phosphatase determinations.

Laboratory Procedures

Calcium, creatinine, acid and alkaline phosphatase levels were measured by standard laboratory procedures. Hydroxyproline was measured after hydrolysis of duplicate specimens from aliquots

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of 24-hour urine collections by the method of Prockop and Udenfriend (1960). The free and peptide-bound fractions were measured together as the total hydroxyproline (THP). In a small group of patients the non-dialysable fraction was assayed on the residue of urine dialysed for 3 days against distilled water through Vysking tubing.

Results

Urine Hydroxyproline Excretion (THP) (Fig. 1)

THP excretion was elevated in all untreated patients with bone metastases diagnosed by bone scan (Group 1). The normal range (15-43 mg/24 hours) was defined in our laboratory for a normal male age-matched population. All patients without bone metastases (Groups 3 and 4) had a normal urinary THP output. The only group of patients with values both within and above the normal range were those with skeletal metastases treated with oestrogens (Group 2). Patients in this group with normal THP levels had all shown improvement of symptoms after treatment for

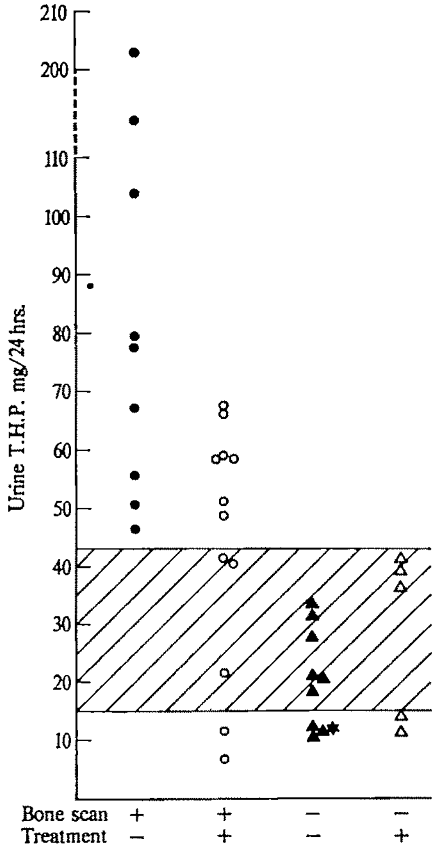


Fig. 1. 24-hour total hydroxyproline excretion in patient with carcinoma of the prostate. Normal range (mean ±2 S.D.). 15-43 mg/24 hrs (shaded area).

Clinical categories: Group 1—Bone scan positive, no treatment
Group 2—Bone scan positive, on hormonal treatment
Group 3—Bone scan negative, no treatment
Group 4—Bone scan negative, on hormonal treatment.

▲* = Patient W. N.—bone scan equivocal, skeletal survey showed osteoarthritis without metastases.

Table I

Serial Measurements of Urine THP (mg/24 hours) in Patients without Bone Metastases on Treatment with Oestrogens

Patient	Pre-treatment	Months on treatment		
		2	4	6
W. N.	12·2	11·6	18·9	5·3
R. P.	31·2	13·4	17·2	13·8
F. H.	11·6	–	11·5	18·3
J. W.	–	44·2	41·4	40·2

J. W.: positive bone scan due to Paget's disease.

at least 2 months. Conversely, some of the patients in Group 2 with elevated THP levels had not had a satisfactory response to treatment. Serial studies showed that after patients had become established on hormone treatment reduction in THP output corresponded to symptomatic improvement, despite the fact that little or no change had occurred in the follow-up bone scan. Similarly, treatment of recurrent skeletal metastases with radiotherapy led to remission of bone pain and fall in THP (Fig. 2). Conversely, relapse was associated with a rise in THP.

2 patients showed an initial rise in THP after the start of hormone treatment. More frequent THP measurements in another patient showed a complex pattern of early changes. THP initially fell then rose to pre-treatment levels. All 3 patients had osteolytic deposits and one showed an unequivocal radiologic response to treatment with intense sclerosis of formerly lytic lesions. Hormone treatment had no consistent effect upon the normal THP levels of patients without demonstrable bone metastases (Table I; Fig. 1). One patient (J. W.) included in Group 2 had serial THP levels at approximately the upper limit of normal. His positive scan was thought to be due to Paget's disease diagnosed on the skeletal X-ray.

The output of non-dialysable peptide bound hydroxyproline was usually unmeasurable. However, 1 patient with osteolytic lesions had values beyond the limits of experimental error. Here levels did not alter with treatment though they increased as a fraction of the THP.

THP Cr Ratio (Fig. 3)

The ratio between THP and creatinine was elevated in most patients with bone metastases compared with the upper limit of normal defined by Guzzo *et al.* (1969). However, some patients without metastases had high values.

Plasma Alkaline and Serum Acid Phosphatase (Formol-stable Fraction) (Figs. 4 and 5)

Both measurements were usually elevated in the presence of metastases demonstrated by bone scans. However, normal levels were sometimes found in patients with untreated metastases. On

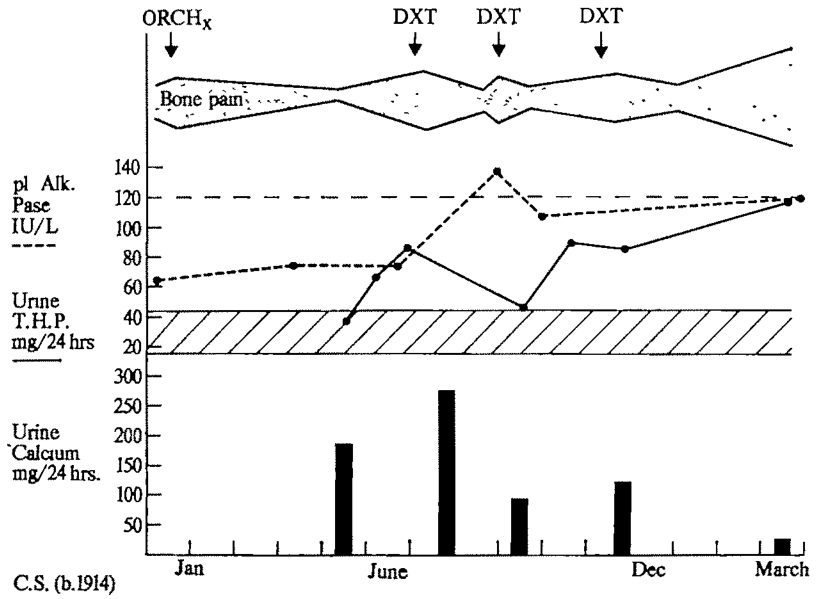


Fig. 2. Patient C. S. Serial changes in 24-hour THP and calcium excretion, plasma alkaline phosphatase (upper limit of normal range 120 i.u./l) and symptomatic response of bone metastases to hormonal treatment or radiotherapy.

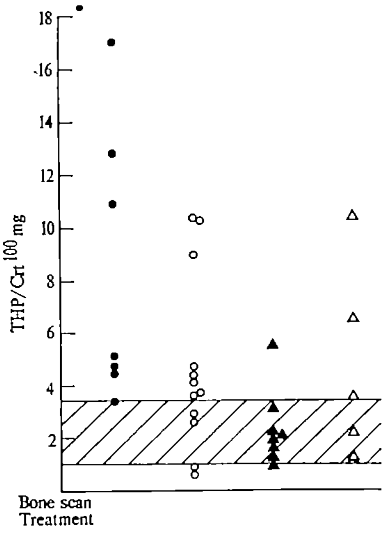
oestrogen treatment more patients had normal plasma alkaline phosphatase levels than THP output. 1 patient with a normal bone scan had elevated plasma alkaline phosphatase which was probably due to liver involvement. Urinary THP in this patient was normal. In the serial studies, plasma enzyme levels tended to reflect the symptomatic effects of treatment and therefore to correspond to changes in THP excretion.

Urine Calcium

24-hour calcium excretion did not discriminate between patients with or without bone involvement. However, in 1 patient with osteosclerotic deposits calcium output fell with symptomatic deterioration and a rise in THP excretion (Fig. 2). Conversely, in a patient with osteolytic deposits urine calcium which was initially elevated, fell with effective treatment.

Discussion

In several previous studies, elevated levels of THP have been described in the presence of bone metastases due to a variety of malignant diseases, including carcinoma of the prostate (Hosley *et al.*, 1966; Bonadonna *et al.*, 1966). However, detailed comparison between THP output and other methods of detection of metastases has only been made by one other group (Kontturi, Sotaniemi and Larmi, 1975). Curiously, in that study, serum non-protein bound hydroxyproline was thought to be a more reliable index than urinary THP, though it is doubtful whether the accuracy of the experimental method would have been sufficient to discriminate individual cases.



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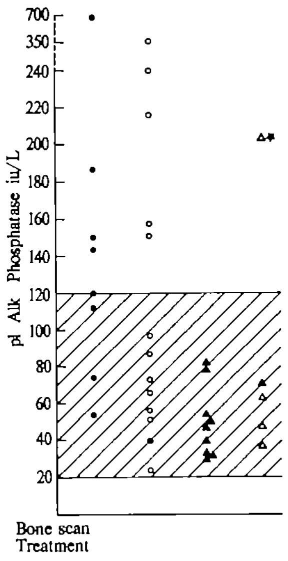

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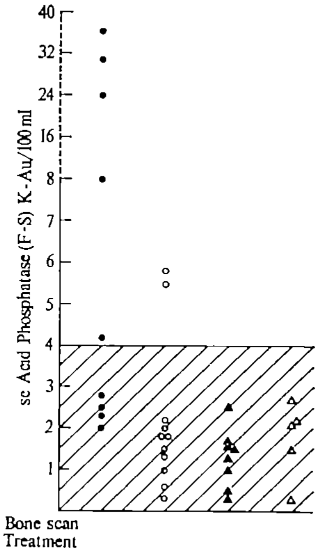

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Fig. 3. 24-hour THP/creatinine ratio × 100 in groups 1-4 (see legend to Fig. 1). Normal range 1-3 4 (Guzzo *et al.*, 1969).

Fig. 4. Plasma alkaline phosphatase in groups 1-4. Normal range 20-120 i.u./l.
△* = Patient A. R.—elevated alkaline phosphatase probably due to liver metastases.

Fig. 5. Serum phosphatase (formol-stable fraction) in groups 1-4. Normal range 0-4 King Armstrong units/100 ml.

We have shown that in untreated patients with carcinoma of the prostate, urine THP was a reliable index of bone metastases demonstrated by bone scanning. Random measurements on patients with bone deposits treated with oestrogens were frequently elevated but when normal the patients were in symptomatic remission. The serial study also tended to confirm that changes in THP rapidly followed effective hormonal treatment or radiotherapy. THP may therefore be a more sensitive quantitative index of activity of bone metastases which are only otherwise diagnosed qualitatively by scanning.

In another study the THP/creatinine ratio measured on a single random urine specimen was found to be as reliable as 24-hour urine THP and has the obvious advantage of not requiring complete 24-hour collections (Guzzo *et al.*, 1969; Powles *et al.*, 1975). However, although there is an overall similarity, we found that the correlation between THP and THP/creatinine on the 24-hour specimens was poor. We have no explanation for this discrepancy but feel that there must have been too great a variation in urinary creatinine between patients in this age-group to allow it to be used as an index of complete collection.

Bone-seeking isotopes localise in newly calcifying collagen and possibly in tumour tissue itself (Galasko, 1972; Lentle *et al.*, 1976). A positive scan may therefore be found in a number of benign conditions, notably in juxta-articular bone involved in degenerative or inflammatory arthritis. THP excretion which is not increased in arthritis may therefore be useful in discriminating such conditions. This was illustrated in one patient (W. N.) whose THP was normal and scan equivocal (Fig. 1).

Urine THP reflects bone collagen turnover, but in metastatic disease this will be predominantly osteolysis (McDonald, Mamola and Henneman, 1965; Bonadonna *et al.*, 1966). However, in other circumstances a non-dialysable peptide fraction in urine may be derived from the production of new collagen (LeRoy *et al.*, 1964). Increased output of these large molecular weight peptides might have been expected in prostatic carcinoma both with the development of osteoblastic metastases and during the healing of osteolytic deposits. This could not be confirmed in the present limited study though in 1 patient with lytic bone metastases the fraction of the THP as dialysable hydroxyproline increased with treatment, possibly indicating healing. The initial rise in THP after the start of treatment of 3 other patients with lytic lesions may also reflect collagen synthetic activity in healing bone metastases.

Alkaline phosphatase was a less reliable index of bone metastases than THP, as many patients had normal levels and positive bone scans. Furthermore, 1 patient without bone metastases has a grossly elevated level (Fig. 3): this was probably due to hepatic involvement by tumour. THP therefore appeared to discriminate bone from liver disease. This application of the measurement of THP has been described elsewhere (Cerda *et al.*, 1970). Serial alkaline phosphatase levels altered predictably and like THP fell in remission and rose during "escape" from hormonal therapy.

Serum acid phosphatase has been regarded as an unreliable index of metastatic disease in prostatic carcinoma, even when more specific iso-enzymes are measured. Theoretically, it should reflect tumour cell activity more closely than THP or bone scanning. However, we have confirmed its unreliability compared with THP excretion.

The improved resolution with the introduction of newer compounds for use in bone scanning, such as Tc-99m-complexes, may ultimately allow quantitative bone scanning from which serial assessments can be made. Techniques for measuring acid phosphatase may be refined further. Until then, THP excretion seems to be a useful practical alternative as a quantitative measure of the presence or progress of bone metastases in carcinoma of the prostate.

Summary

24-hour urinary hydroxyproline excretion (THP), a marker of bone collagen metabolism, has been measured in 35 patients with carcinoma of the prostate. 21 patients had bone metastases diagnosed by bone scanning (^{99m}Tc MDP).

All 9 patients with metastases studied before hormonal treatment and the majority of those on treatment had elevated levels. Patients with negative bone scans invariably had normal THP levels. Furthermore, THP reflected the presence of bone metastases more accurately than plasma alkaline or acid phosphatase. Serial THP levels altered predictably with symptomatic response to treatment.

These results suggest that THP is more reliable than other markers of the presence and activity of bone metastases in response to treatment and may have been neglected in favour of more elaborate and costly X-ray and isotope investigations.

We are indebted to Dr Roger Smith for helpful advice and research facilities and to Mr J. C. Smith for referring his patients to us.

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The Authors

M. C. Bishop, MD, FRCS, Lecturer in Surgery.
G. J. Fellows, MS, FRCS, Consultant Urologist.

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The Treatment of Oestrogen-Escaped Carcinoma of the Prostate with Estramustine Phosphate

G. D. CHISHOLM, E. P. N. O'DONOGHUE and C. L. KENNEDY
Hammersmith Hospital and St Peter's Group of Hospitals, London

When androgen suppression, by either stilboestrol or orchidectomy, was introduced for carcinoma of the prostate the good response in most patients tended to obscure that small proportion who never responded at all. The management of these primary non-responders and of those who show a good initial response but then develop further symptoms due to progression of the disease has been mainly palliative using either analgesics or radiotherapy. Attempts at further hormonal control by other antiandrogens or adrenalectomy have been disappointing though hypophysectomy continues to be valuable in the treatment of widespread bone pain.

The results with chemotherapy for advanced prostatic cancer have been discouraging. Few drugs have been shown to have any effect on this tumour (Wassermann *et al.*, 1975) and co-operative trials are in progress to evaluate those that are available.

Estramustine phosphate (Estracyt) is a nor-nitrogen mustard bound to oestradiol-17-phosphate. It has been suggested that the steroid fraction acts as a carrier to hormone-dependent tumour tissue where the alkylating agent is released and exerts a direct action (Muntzing *et al.*, 1974). Earlier reports showed an encouraging response in advanced disease (Alfthan and Rusk, 1969; Jonsson and Hogberg, 1971) and subsequent reports have continued to show a useful clinical response (Fossa and Miller, 1976; Mittleman, Shukla and Murphy, 1976; Nagel and Kolln, 1977).

We have studied the value of estramustine phosphate in a group of patients all of whom had developed objective evidence that they were no longer controlled by oestrogens, so-called "oestrogen-escape".

Patients and Methods

The following were the requirements for entry to this study:

1. Histologically confirmed carcinoma of the prostate.
2. Previous oestrogen and/or orchidectomy treatment.
3. No previous radiotherapy.
4. No previous cytotoxic therapy.
5. No other malignant tumour.
6. Expected to live more than 90 days.
7. Objective evidence of progression of disease as judged by
    radioisotope bone scan
    skeletal X-ray survey
    serum acid phosphatase
    prostatic obstruction
    lymphatic obstruction.

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

Dosage

All previous oestrogen treatment was stopped. Estramustine phosphate was given orally 280 mg t.d.s. which approximates to the optimum tolerated dose (Muntzing *et al.*, 1974). 1 patient received an intravenous dose of 300 mg per day for 3 weeks.

Assessment of Response

Treatment was started while all patients were in hospital so that their initial response could be monitored. Upon discharge from hospital, most patients were seen at 1-month intervals because of the proportion that developed gastrointestinal side-effects. We used the criteria for response recommended by the National Prostatic Cancer Project (Mittleman *et al.*, 1975):

(i) *Partial Objective Response*

1. A 50% reduction in measurable or palpable soft tissue tumour when present.
2. Return of an elevated serum acid phosphatase to normal.
3. The recalcification of some osteolytic lesions if present.
4. No increase in size of pre-existing lesions and no new areas of malignant disease appearing.
5. No significant deterioration in weight (greater than 10%), symptoms or performance status (1 score level).

(ii) *Subjective Response*

(*a*) Performance status—0. Normal activity
1. Symptoms, but ambulatory
2. Bedridden <50% of time
3. Bedridden >50% of time
4. 100% bedridden

(*b*) Appetite
(*c*) Weight
(*d*) Pain.

Histological Grade

The initial histology on 29 patients was reviewed by Dr K. M. Cameron, Institute of Urology; sections from 1 patient were not available:

Grade 1 (well differentiated)	3
Grade 2	14
Grade 3 (anaplastic)	12

Results

Side-effects

16 patients received their full dosage for a minimum of 3 months and 2 of these complained of nausea and anorexia. The remaining 14 stopped the drug within 3 months—in 5 because of gastrointestinal effects, in 6 because of progression of the disease and in 2 who died. 1 patient developed oedema of the tongue and mouth which was interpreted to be an allergic reaction.

Toxicity

There were no changes in either the white blood count or the liver function tests.

Partial Objective Response

According to the criteria used for this response, there were 8 patients (27%) who showed no progression of the lesion and no change in symptoms or performance status. No patient had a serum acid phosphatase that returned to normal although 2 showed definite trends in that direction.

Subjective Response

10 patients (33%) had a subjective response, mainly in terms of pain which also improved the performance status. This response was sustained in only 1 patient and he remains on treatment after 14 months.

Overall Results

8 of the 30 patients remain alive and only 1 continues to receive estramustine phosphate. 3 of these patients have had an hypophysectomy and this was followed by a remission of symptoms. 1 has received radiotherapy to areas of pain in bones and 3 are receiving symptomatic drug treatment only. 22 patients have died after an average survival of 7 months; all died from the primary tumour.

Discussion

Although the partial objective response rate was 27% and the subjective response rate was 33%, it has been evident from this study that the use of an objective measure that includes "steady state", "no change" or "objectively stable" (Scott *et al.*, 1975) as a positive response, greatly affects the apparent value of a drug. In this series, no patient showed a satisfactory objective response and if the "steady state" is excluded no patient had a partial objective response. The reliability of a subjective assessment is always open to question and it is possible that palliative symptomatic treatment might have achieved the same "steady state" response seen in this series.

Thus, while our results are very similar to those recently reported by Mittleman *et al.* (1976) there was no convincing or sustained response to estramustine phosphate. We re-examined the histological grade in this series lest there was a preponderance of aggressive anaplastic tumours; while most tumours are grade 2/3 it seems unlikely that this could explain the lack of response.

We have also reconsidered serum acid phosphatase levels. Only 12 of the 30 patients had an elevated value but only 4 were greater than 10 King Armstrong units (K.A.U.) and the highest was 63·0 K.A.U. It is possible that these relatively low values indicate a group of tumours unlikely to be affected by this drug. However, even those few with raised values showed no evidence of a response that differed from the remainder.

This study illustrates the difficulties of defining cases to be studied, in measuring response and in interpreting results that can be attributed to a chemotherapeutic agent. The most careful of definitions and rules for a study can lead to results which, out of context, can be misleading. The use of a definition of response that includes a "steady state" or "objectively stable" can be questioned. A drug that requires such assistance to produce a positive result cannot be acclaimed a therapeutic success. Indeed, any drug with a 20 to 30% response also has a 70 to 80% non-response.

It could be argued that any small response is valuable to a patient. This could be true provided that the side-effects are minimal. In the present study more than half of the patients developed gastro-intestinal symptoms and many stopped the drug because of this. These were not serious side-effects as judged by the incidence in other reports using powerful chemotherapeutic drugs and there is no doubt that such effects can become acceptable if the result is also acceptable (Burchenal, 1976).

In studying the role of any new drug, 3 phases must be assessed. Phase 1 is a preliminary study, usually in patients with advanced disease, to ensure that the drug is not unduly toxic. Phase 2 is a screening procedure to determine if a therapeutic regimen is sufficiently effective in treating a disease to warrant further study. We have concluded from this Phase 2 study that estramustine phosphate produces a palliative response in a small proportion of oestrogen-escaped patients. However, in order to establish its true value compared with other treatments, controlled randomised trials are necessary—Phase 3 studies—such a study is now in progress by the National Prostatic Cancer Project (NPCP) in the US.

The role of estramustine phosphate for primary treatment is being studied in co-operative trials. In our limited experience the initial response has been comparable to conventional oestrogen therapy.

Summary

30 patients with oestrogen-escaped carcinoma of the prostate have been treated with estramustine phosphate (Estracyt). 27 % showed a partial objective response and 33 % had a subjective response.

The terms used for defining a response are challenged and it is recommended that comparative controlled trials are necessary to judge the place of this drug in the management of advanced prostatic cancer.

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The Authors

G. D. Chisholm, ChM, FRCS, Senior Urological Surgeon and Senior Lecturer.
E. P. N. O'Donoghue, FRCS, Senior Lecturer and Consultant.
C. L. Kennedy, FRCS, Urological Registrar.

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Choice of Operation to promote Micturition after Spinal Cord Injury

G. J. FELLOWS, I. NUSEIBEH and J. J. WALSH
National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury, Bucks

Following injury to the spinal cord, retention of urine is the rule, necessitating some form of catheter drainage. Micturition is re-established in the majority of patients within the first 3 months after injury. Parasympathomimetic and alpha-adrenergic blocking drugs may help to initiate micturition. There remains a group of patients who fail to void and require either permanent catheters or surgery to lower the resistance of the bladder outflow tract.

The operations most frequently employed are internal membranous urethrotomy (external sphincterotomy, IMU), bladder neck resection (BNR) or a combination of the two (BNR+IMU). An inappropriate operation will be ineffective and may lead to undesirable complications. Bladder neck resection is followed by retrograde ejaculation (most patients with cord injury are young men) and internal membranous urethrotomy occasionally causes erectile impotence (Schoenfeld, Carrion and Politano, 1974; Thomas, 1976).

This paper sets out to determine whether the result of surgery can be predicted in the individual patient, thus enabling the correct operation to be chosen.

Patients and Methods

From June 1974 to September 1976 61 male patients who had not established satisfactory micturition after injury had one of the following operations: IMU (15), BNR (22), BNR+IMU (24). 31 had complete urinary retention and 30 could pass a little urine with difficulty, leaving residual urine volumes in excess of 150 ml. Cord injury was traumatic in 54 and due to benign lesions with or without surgery to the spine in 7. One-quarter had incomplete lesions.

The following factors which might influence the outcome of surgery were studied: age, level of lesion, sacral cord reflexes, cystometry, urethral pressure profile and the appearance of the bladder neck on cystourethrography. All patients had full neurological examinations, intravenous urograms and cystourethrograms preoperatively. 30 patients had preoperative cystometrograms. Bladders were filled through an 8 Ch urethral catheter at 50 ml per min to a capacity not exceeding 500 ml. Total bladder, rectal and subtracted pressures were recorded. Detrusor contractions were triggered if possible by coughing, suprapubic tapping and other manoeuvres, such as anal stimulation. Urethral pressure profiles were obtained in most patients who had cystometrograms. Bladder neck resection was usually from 3 to 9 o'clock using a loop electrode, occasionally the resection was continued around the whole circumference of the bladder neck. Internal membranous urethrotomy was performed with a Collings Knife Electrode at 3 and 9 o'clock from the level of the verumontanum distally not less than 2·5 cm. The operation was termed successful if micturition occurred with a residual volume less than 100 ml. In most patients it was much less and in many was nil.

Results

The overall results after each operation are shown in Table I. The superiority of BNR+IMU over BNR alone falls just short of statistical significance. A second operation was carried out in all

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but 3 of the failures and there was only 1 patient who failed to void after a second operation. Thus 4 patients out of the original 61 were finally assigned to catheter drainage.

Younger patients fared neither better nor worse after surgery than older patients (Table II).

3 tetraplegic patients had BNRs and all failed to void (Table III). When the upper sensory level was L1 or below, all patients passed urine whatever operation was employed. The remaining patients had lesions in the thoracic segments. The three failures after IMU all occurred in patients with lesions above T6 (above the sympathetic outflow to the bladder). There were failures above and below this level following BNR and the combined operation.

The integrity of sacral cord segments S2, 3, 4 was tested by the anal and bulbo-cavernosus reflexes and confirmed by penile erections. The overall results of surgery were better in those with absent sacral reflexes ($P < 0{\cdot}05$) (Table IV). The combined operation was superior to BNR alone in those with intact sacral reflexes ($P < 0{\cdot}05$) but not significantly better than IMU.

The strength of detrusor contractions did not correlate with the outcome of surgery after any of the three operations (Table V).

Maximum closure pressure on the urethral pressure profile varied from 36 to 140 cm of water (Table VI). The 3 patients with the highest pressures (111, 123, 140 cm of water) all failed to void after bladder neck resection alone.

Cystograms with films during attempted micturition were obtained in all patients. In 19 the bladder neck appeared normal. In 33 patients it remained closed. In the remaining 9 a thin trickle of contrast entered the urethra with no funnelling of the bladder neck. These patients are classified with the "closed" group in Table VII. The appearance of the bladder neck was no guide to the outcome of surgery.

Discussion

During the period of this survey, approximately 30% of men with new lesions admitted to the National Spinal Injuries Centre had surgery to their bladder outflow tracts. This is similar to the proportion reported by O'Flynn (1974).

When surgery is necessary there are no agreed criteria for resecting the bladder neck, incising the membranous urethra or combining the 2 operations as advocated by Smith, Cook and Arrowsmith (1971).

Gibbon (1974) states that the bladder neck should open if detrusor contractions exceed 30 cm of water. Rossier and Ott (1974) add bladder neck resection to internal membranous urethrotomy if detrusor pressure is low. We have failed to confirm this relationship between detrusor pressure and the result of IMU although our numbers are small. There were, however, 3 unexpected failures after IMU in patients with strong detrusor contractions (>30 cm H_2O). It may be significant that the 3 patients with the highest maximum urethral closure pressures failed to void after BNR alone. A high pressure in the membranous urethra may be an indication for IMU.

Electromyography of the external sphincter has not been performed in this series. Detrusor sphincter dys-synergism demonstrated by synchronous cystometry and sphincter electromyography may be an indication for IMU (Thomas, Smallwood and Graham, 1975). However, patients may have significant resistance in the membranous urethra without external sphincter spasm and also require "sphincterotomy" (Abel *et al.*, 1974). Sphincterotomy (IMU) was first used in patients whose sacral cord reflexes had been abolished by alcohol block (Ross, Gibbon and Damanski, 1958).

It might be expected that the voiding cystourethrogram would be a sound guide to the choice of operation, those with closed bladder necks responding well to BNR and those with wide bladder necks to IMU. The present study, however, shows that the appearance of the bladder neck is no help in the choice of operation. Others have also found cystourethrography unreliable (Shopfner, 1967; Scher, 1977).

The opinion that younger men are more likely to pass urine after surgery than older men was not confirmed.

Table I

Result of First Operation after Cord Injury

	Total	Success	Failure
IMU	15	10	5
BNR	22	12	10
BNR+IMU	24	19	5

IMU—Internal membranous urethrotomy
BNR—Bladder neck resection

Table II

Age in Relation to Result of Procedure

	Success	Failure
IMU	31 (18-46)	31 (17-65)
BNR	44 (20-69)	43 (21-62)
BNR+IMU	37 (17-56)	41 (17-59)

Mean age in years with range in parenthesis.

Table III

Upper Level of Neurological Lesion

	Cervical		Thoracic		Lumbo-sacral	
	Success	Failure	Success	Failure	Success	Failure
IMU	4	2	5	3	1	0
BNR	0	3	6	7	6	0
BNR+IMU	2	2	14	3	3	0

Table IV

Integrity of Cord Segments S2, 3 and 4

	Intact		Disrupted	
	Success	Failure	Success	Failure
IMU	6	5	4	0
BNR	7	9	5	1
BNR+IMU	17	5	2	0

The overall failure rate after BNR alone is unacceptably high. It is probably an inappropriate operation in patients with cervical lesions and in patients with maximum urethral closure pressure in excess of 100 cm of water, but may be suitable in patients with low lesions and low pressure in the membranous urethra. Bladder neck resection should be avoided if the patient is able to ejaculate. Internal membranous urethrotomy appears to be a suitable operation for patients with lesions at all levels of the spinal cord. If this operation fails, the completeness of the IMU can be checked by repeating the urethral pressure profile (Abel *et al.*, 1975). IMU can be repeated or, if necessary, a bladder neck resection can then be performed. The combined operation under one anaesthetic carries the greatest chance of success, and should be performed if no attempt is to be made to preserve sexual function.

Summary

61 male patients who had resection of the bladder neck alone, internal membranous urethrotomy alone or a combination of the 2 procedures to establish micturition after cord injury are reviewed.

Table V

Detrusor Contractions on Cystometrograms

	More than 20 cm water		Less than 20 cm water	
	Success	Failure	Success	Failure
IMU	2	3	2	0
BNR	3	2	4	4
BNR+IMU	2	0	6	2

Table VI

Mean Maximum Urethral Closure Pressures

	Success	Failure
IMU	60 (4)	67 (2)
BNR	66 (6)	125 (3)
BNR+IMU	78 (6)	84 (3)

Figures in parentheses are numbers in each group.

Table VII

Bladder Neck on Cystography

	Wide		Narrow/closed	
	Success	Failure	Success	Failure
IMU	4	3	6	2
BNR	4	2	8	8
BNR+IMU	5	1	14	4

The combined operation has the greatest chance of initial success and should be performed if no attempt is to be made to preserve sexual function.

Internal membranous urethrotomy is appropriate for lesions at all levels of the cord.

Cystometry and cystourethrography are not helpful in the choice of operation.

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The Authors

G. J. Fellows, MS, FRCS, Consultant Urologist.
I. Nuseibeh, FRCS, Consultant Surgeon.
J. J. Walsh, MD, FRCS, FRCP, Director of National Spinal Injuries Centre.

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Direct Vision Urethrotomy in the Management of Urethral Strictures

H. LIPSKY and G. HUBMER

Department of Urology, University of Graz, Austria

Transurethral incision of urethral stricture is an old method of treatment. Maisonneuve (1854) and Otis (1872) invented urethrotomes which are still used today (Matouschek and Michaelis, 1975). These instruments are passed blindly and the stricture is cut without vision. These urethrotomes can only be used if the calibre of the stricture is wide enough to admit them. Direct-vision urethrotomy with electric diathermy was tried by Ravasini (Ravasini, 1957). In 1971 Sachse designed a new instrument with a sharp blade which could cut the stricture under direct vision. He treated a large series of patients with this method and reported a success rate of 80% (Sachse, 1974). Since then other series have been published reporting similar success (Elsässer *et al.*, 1974; Matouschek and Michaelis, 1975).

Patients and Method

We have managed a series of 32 patients with direct-vision urethrotomy. Their age ranged from 17 to 82 years (average 43 years). The aetiology and the site of the strictures are shown in Tables I and II. None of the patients had urinary infection at the time of operation but 60% had had a urinary infection at some time. 8 patients had undergone intermittent dilatation for several years.

The procedure was carried out in 30 patients under general and in 2 patients under local anaesthesia.

Technique

The procedure starts with urethroscopy, which is done with the urethrotome. The instrument is so designed that a ureteric catheter can be passed through the stricture under vision. When the ureteric catheter is in the bladder the instrument is withdrawn and inserted again beside the catheter. This provides greater mobility for the cutting manoeuvre. The stricture is cut at 12 o'clock along the catheter. It is necessary to cut through all scarred tissue until the instrument passes though the stricture easily. If the stricture is too narrow or it is impossible because of technical reasons to pass a ureteric catheter, the operation can be tried without it. However, there is always the danger of a false passage. Irrigation is done with an isotonic solution since absorption into the venous spaces of the corpora cavernosa is always possible. Minor extravasation of irrigation fluid is harmless. If the incision is at 12 o'clock an injury of the corpora cavernosa will be avoided and no major bleeding will occur. In all our patients a silicon catheter (22F) was inserted after urethrotomy.

Postoperative Treatment

An antibacterial agent was given to all patients. Many patients were discharged from the hospital on the third day with an indwelling catheter. Catheters were left indwelling for 5 to 14 days and

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Table I

Aetiology of 32 Strictures

Inflammatory	10
Traumatic	8
Iatrogenic	6
Congenital	3
Unknown	5

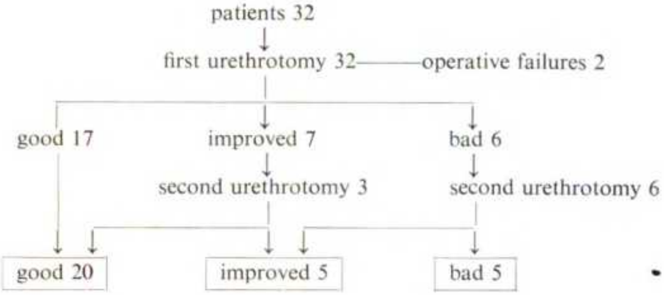
Table II

Site of 32 strictures

Penile	10
Bulbar	18
Membranous	4

Table III

Results of Direct-vision Urethrotomy



on removal the patients were advised to practise "hydraulic self dilatation" for 6 months. They were told to compress the glans during micturition in order that a dilatation of the whole urethra would occur. Weekly instillation of steroid jelly was done in 10 patients.

Complications

In 2 patients with penile strictures it was not possible to pass a ureteric catheter before the operation. The ensuing urethrotomy resulted in a false passage with massive extravasation of irrigation fluid. The procedure was stopped and the first stage of a conventional urethroplasty was carried out. Both patients had an uneventful course. Minor bleeding subsided quickly after the catheter had been inserted. Serious bleeding, fever and epididymitis were not seen in this series.

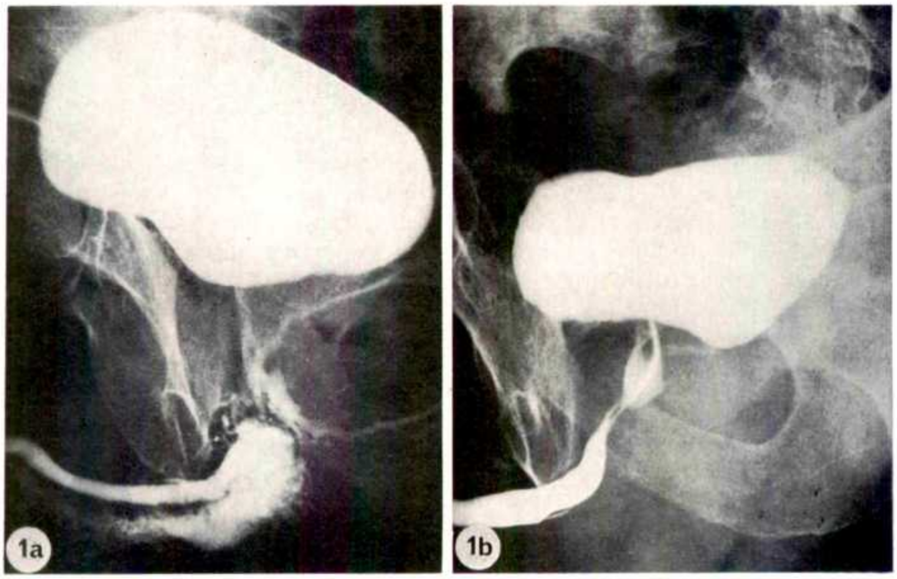


Fig. 1. Sch. V., 70 years old. Stricture of unknown aetiology in the membranous part of the urethra. (*a*) Before treatment; (*b*) 16 months after urethrotomy.

Results

The duration of follow-up varied from 9 months to 3 years. The assessment comprised urinalysis, history, flow-rate, retrograde urethrography and in some patients urethral calibration with a soft catheter of 16 F calibre. Flow rates of 15 ml per sec or more with a normal urethrogram were regarded as a good result (Group I). Patients with improvement of symptoms and flow-rates from 8 to 15 ml per sec were regarded as improved. All patients of this group had some degree of re-stenosis in the strictured area (Group II). Patients with recurring symptoms and a poor stream had a considerable re-stenosis of the stricture. They were regarded as bad results (Group III). On assessment there was a surprisingly close correlation between symptomatology and flow-rates. In some patients there was a discrepancy between the urethrography and urethral calibration, radiologically narrow urethras admitted catheters from 16 to 18F without difficulty.

All recurrences were evident within a period of 3 months. In 20 patients the results were good, 5 were improved and in 5 patients there was a bad result. In 9 patients a second procedure was necessary to obtain these results (Table III).

Discussion

Successful operative repair of urethral stricture can be carried out with several techniques. The results of these procedures are satisfactory showing good results in up to 90% (Schmiedt, 1973; Blandy *et al.*, 1976). In spite of these good results there remain in all urological units a certain number of patients who have intermittent dilatation for their stricture. The reason for this is either the advanced age of a patient or his refusal of a 2-stage operative procedure.

Direct-vision urethrotomy can be performed easily and without major risk in all patients. Many centres perform this procedure on an out-patient basis with local anaesthesia. The results compare favourably with those of open surgery. If re-stenosis occurs, urethrotomy can be repeated without appreciable risk to the patient or the local situation. Conventional urethroplasty can always be carried out at a later date. However, the method has its clear limitations, the most important

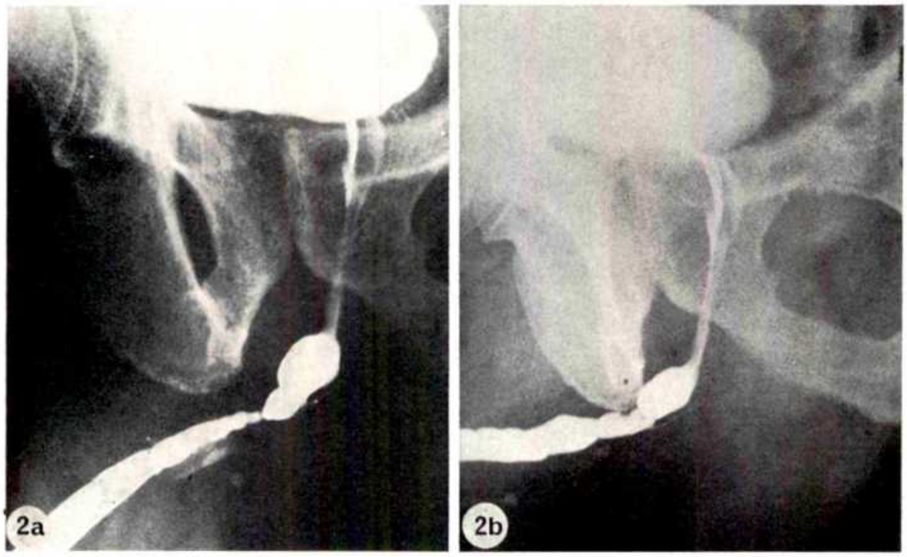


Fig. 2. L. J., 72 years old. Inflammatory stricture in the penile and bulbar part of the urethra. (*a*) Before treatment; (*b*) 12 months after urethrotomy.

being the length of the stricture. A stricture longer than 3 cm is liable to recur within a short time· Traumatic strictures with dense scar tissue have also a tendency to re-stenose. The ideal indication for urethrotomy is a short stricture with no inflammatory changes, which has never been dilated.

Strictures in the membranous part of the urethra may raise problems with postoperative continence. In order to avoid this complication a cautious incision of the stricture only up to 22F is advised (Sachse, 1974). Cutting without a ureteric catheter *in situ* can be tried, but there is always the danger of incising a false passage. Other authors have carried out urethrotomy in patients with complete stenosis of the urethra. They cut the urethra against a metal sound which is inserted via a cystostomy from the bladder into the posterior urethra. We have no experience with this technique.

The postoperative care of urethrotomy is handled differently by most authors. The need for a postoperative catheter and the period of catheterisation differ and are discussed. The period varies from 8 to 21 days. Our usual practice was to remove the catheter after 1 week. There exists general agreement upon the value of hydraulic self-dilatation. The patient must perform this regularly over a long period. We advise that this should be continued for 6 months. If the patient does not understand this or is not cooperative, re-stenosis will very likely recur. The value of postoperative instillation of steroid jelly is not certain. Recently, Sachse reported a method of postoperative management which does not use a catheter after operation. In order to avoid adhesion of the urethral wound, steroid jelly is instilled into the urethra by the patient after micturition. The jelly is kept in place by a specially designed ribbon which is wrapped around the glans penis. With this form of management, Sachse also claims good results in longer strictures (Sachse, 1977).

Summary

A series of 32 patients underwent direct vision urethrotomy.

The technique is simple and the stay in hospital short. Intra- and postoperative complications are rare.

Postoperatively, a silicon catheter is left for approximately 7 days, then hydraulic self-dilatation is performed by the patient for 6 months.

25 patients in this series (83%) voided satisfactorily after the procedure and needed no further treatment.

Unsatisfactory results were obtained in patients with long strictures, in traumatic strictures with large scarred areas and in patients who failed to carry out regular hydraulic self-dilatation.

We advise direct-vision urethrotomy as a treatment of choice for urethral strictures which do not exceed a length of 3 cm.

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The Authors

H. Lipsky, MD, Univ. Doz. for Urology.
G. Hubmer, MD, Professor of Urology.

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Light and Electron Microscopy Study on Urethral Regeneration

SAID I. HAKKY
Hammersmith Hospital and Royal Postgraduate Medical School, London, England

The urothelium has a remarkable ability to regenerate and the mechanism that maintains or controls the process remains unknown. Swinney, Tomlinson and Walder (1961) studied bladder substitution and Blandy (1961) used a segment of ileum (having removed the mucosa and submucosal portion); later these segments were found to be fully lined by transitional epithelium which appeared to have grown in from the implanted ureter. Sporadic cases have been reported in the literature where a segment of the urethra has been replaced by a tube of silicone rubber or polyethylene (de Nicola, 1950; Foret, 1950). Nowadays urethroplasty using either skin flaps or a free skin graft is accepted as the correct treatment for urethral stricture. However, there are instances where either this is impossible to carry out or a multi-staged procedure is not accepted by the patient. The present experimental work was undertaken to see if a wide-mesh siliconised Dacron could be used as a scaffold for subsequent autogenous urethral replacement by the ingrowth of epithelium.

Material and Method

15 adult male greyhound dogs of approximately the same age and weight were used. All had a normal preoperative urethrogram and sterile urine on culture. In these dogs no less than 5 cm of mid-urethra was excised and replaced by a wide-mesh siliconised Dacron tube 5 cm by 4 mm. The siliconised rubber rod acting as a splint for the Dacron was discarded and replaced by an indwelling catheter (size 10F) for 2 weeks.

Results

1. Immediate

3 dogs developed a fistula to the scrotum in the first 24 hours. After sacrifice at 48 hours the catheter was found to be kinked in 2, while in the third dog the catheter was missing.

2. At 8 Weeks

In the remaining 12 dogs the urinary stream began as just a dribble after removal of the catheter at 2 weeks, but returned to a normal stream within 4-6 weeks except in 1 dog whose stream continued to be poor and he was sacrificed at 8 weeks. In this dog the bladder was found to be distended by 250 ml of retained urine. The bladder wall showed early trabeculation and the regenerating urethra was narrowed along its entire length. The regenerated urethra was lined by an aberrant epithelium, resembling squamous metaplasia of the expected transitional epithelium. The epithelial growth had been so exuberant that the urethral lumen was narrowed and at 1 area the epithelium actually bridged the lumen (Fig. 1).

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3. At 3 and 7 Months

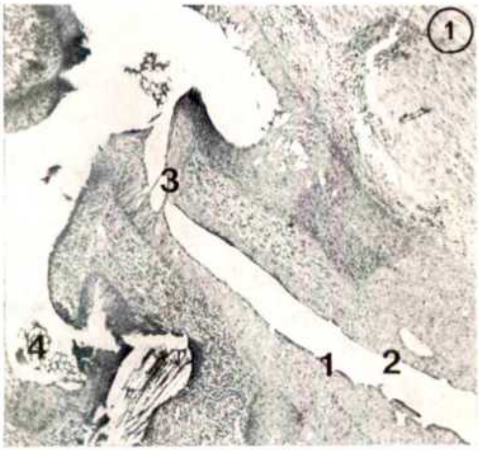
10 dogs were sacrificed. All urethrograms showed an apparent narrowing of the grafted area but without urethral dilatation proximally, or evidence of chronic urinary retention. Macroscopically the Dacron mesh had been extruded into the lumen of the urethra and was only loosely attached to the new urethra; this appeared to account for the apparent narrowing of the urethra on the urethrogram. The diameter of the new urethra was similar to the rest of the urethra and ranged from 3·5 to 4 mm.

Light Microscopy

The normal urethra in dogs is lined by either transitional or stratified cuboidal epithelium and in the subepithelial layer there are collagen fibres, fibroblasts and blood vessels. Occasional cellular infiltration by round cells may be seen (Fig. 2). In the experimental dogs at 3 and 7 months, the epithelium had grown underneath the Dacron graft, thus extruding the graft into the lumen of the urethra with only a loose attachment to the newly regenerated epithelium. The regenerated epithelium was multi-layered with darkly stained nuclei and the overall pattern of this regenerated epithelium was that of an attempt to copy the original excised urethra. In the subepithelial layer, there was an abundance of collagen fibres, fibroblasts, blood vessels, monocytes, lymphocytes, polymorphonuclear leucocytes and foreign body giant cells. This cellular infiltration was notably less at 7 months than at 3 months (Fig. 3). There was no evidence of regenerated cavernous tissue or muscle.

Electron Microscopy

In the normal urethra of a dog, 2 different types of cell are recognised, a basal cell layer of darkly stained convoluted nuclei with a dense band of heterochromatin and a superficial cell layer with much larger nuclei, lighter cytoplasm and nuclei that are not so convoluted. In addition to these cell types there is another cell, having an intermediate morphology but secretory in function (Fig. 4). Few nerve endings are present in the epithelial and subepithelial layer. In the subepithelial layer collagen fibres, fibroblasts, and blood vessels are present.



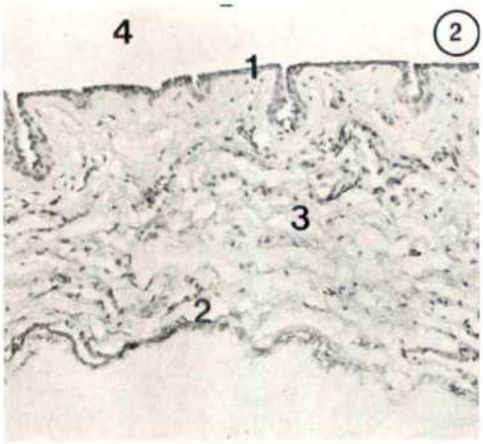
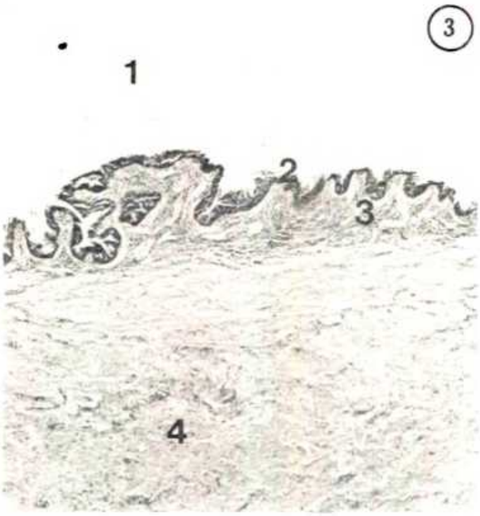


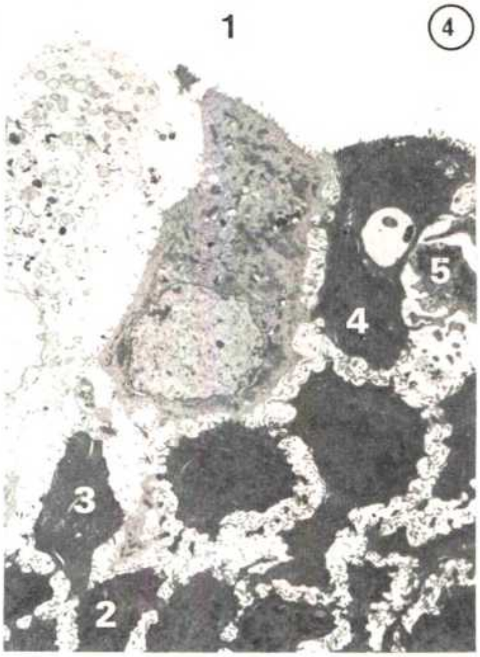
Fig. 1. 8 weeks after urethral replacement: (1) aberrant epithelium, (2) encroaching on lumen of urethra, and at one point (3) aberrant epithelium is crossing lumen of urethra. (4) Dacron graft extruded by the epithelium into the urethral lumen. H & E. ×60.

Fig. 2. Normal mid-urethra of a dog: (1) cobble stone transitional epithelium, (2) cavernous tissue, (3) collagen fibres, (4) urethral lumen. H & E. ×150.

In the regenerated urethra very few of the expected superficial cells were present although the basal cell type was present both along the basement membrane and more superficially. These cells were widely separated and cellular infiltration (mostly lymphocytes) was frequently seen in between these epithelial cells. There were few secretory-type cells, and a very small amount of secretory element was noted after 7 months' observation (Fig. 4).

In the subepithelial layer there was an abundance of collagen fibres, fibroblasts, blood vessels and cellular infiltration. No nerve endings or fibres were seen after 7 months' observation and there was no evidence of regeneration of muscle or cavernous tissue.





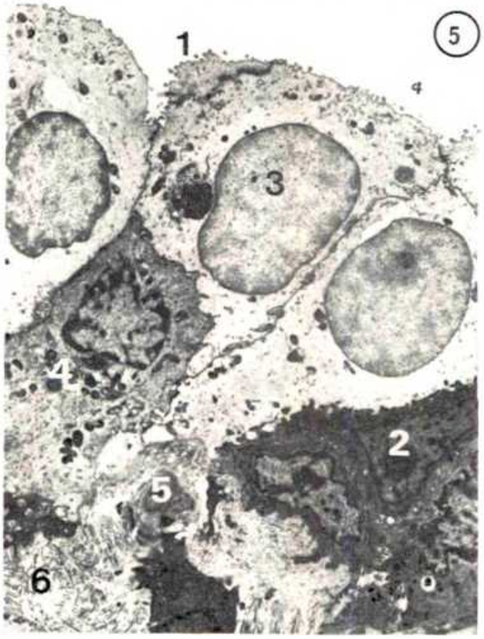


Fig. 3. 7 months after urethral replacement: (1) urethral lumen, (2) hyperplastic epithelium, (3) cellular infiltration, (4) abundant fibrous tissue. No cavernous tissue regeneration. H & E. × 60.

Fig. 4. 7 months after urethral replacement: (1) urethral lumen, (2, 3 and 4) basal cell type, (5) cellular infiltration. × 3,000.

Fig. 5. Normal mid-urethra of the dog: (1) urethral lumen, (2) basal cell type, (3) superficial cell type, (4) intermediate cell type, (5) a nerve fibre at the subepithelial layer, (6) Subepithelial layer. × 3,000.

Discussion

The regenerated epithelium in the experimental dogs was of transitional type in all but 1 dog, whose squamous metaplasia is difficult to understand.

The extrusion of a prosthesis by urothelium is well documented. Bohne, Osborn and Heitle (1955) used an acrylic solid mould for bladder substitution, Swinney *et al.* (1961) used Teflon fabric and Stanley *et al.* (1972) used a silastic prosthesis. In all of those experiments, as well as in the present studies, the epithelial behaviour was essentially the same: the epithelium grew outside the prosthesis, thus extruding the graft into the lumen of the urethra or bladder. There may be 2 explanations for such behaviour. Firstly the role of lymphocytes in the interstitial tissue is still not clear, although it is widely believed that their aggregation is a response to foreign material. The presence of lymphocytes around the Dacron mesh might suggest that they have recognised the foreign material and are actively directing the epithelium for the process of its extrusion. Secondly, the electrical surface charge in the Dacron is such that the epithelium, also with surface charge, has regenerated away from the graft. There is no obvious evidence in this current investigation to indicate which of these 2 is the main cause for such epithelial behaviour.

Bohne *et al.* (1955) noted regeneration of smooth muscle, but in this present study, from both light and electron microscopy, there was no evidence of regeneration of cavernous tissue, muscle or nerve. The abundance of collagen fibres and fibroblasts appeared not to encroach on the urethral lumen after 7 months nor to produce narrowing of the lumen.

It may be concluded that the use of a wide-mesh siliconised Dacron has a place in urethral replacement and currently this form of urethral replacement is being carried out on a group of selected patients.

Summary

In a series of experiments on dogs, it was feasible to replace a segment of urethra using wide-mesh Dacron.

Light and electron microscopy study on the regenerated urethra showed no evidence of muscle, cavernous tissue and nerve regeneration.

Although an excess of fibrous tissue surrounded the regenerated urethra, there was no change in the calibre of the new urethra after 7 months' observation.

I wish to acknowledge the help of Professor J. S. Calnan, President Ahmed Hassan Al-Baker, the President of Iraq. Mr. Tayeh Abdul Karium, the Minister of Oil, for financial assistance. Dr. L. M. Franks of the Imperial Cancer Research Fund. Mr. Taha Ahmed Al-Dawood the Ambassador, and Mr. Khirala Al-Hadithi, First Secretary (Consul), for their help.

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The Author

Said I. Hakky, FRCS(Ed), Senior Surgical Registrar and Tutor.

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Carcinoma of the Penis: a Review of 42 Cases

P. STEWART ORR, T. HABESHAW and R. SCOTT
Department of Urology, Royal Infirmary, Glasgow; Institute of Radiotherapeutics (Belvidere), Glasgow

Cancer of the penis is a condition showing wide racial and geographical variation (Campbell and Harrison, 1970).

In Western society it is an uncommon condition accounting for less than 1% of male cancers (Whitmore, 1970; Hanash *et al.*, 1970) as compared with Eastern countries where figures as high as 30% in Ceylon have been quoted (Cooray, 1944). Due to the low incidence of the disease in the United Kingdom few people are able to gain extensive experience in the treatment of carcinoma of the penis.

Some authorities consider carcinoma of the penis to be a radiocurable disease (Vaeth, Green and Lowy, 1970). This form of therapy allows local control with preservation of function. The present series attempts to evaluate radiotherapy as compared with surgery in the primary treatment of the condition.

Patients and Methods

42 cases treated between 1963 and 1976 (14 years) were examined retrospectively. Where death had occurred (20 cases) the cause was confirmed. In 1 patient the cause of death was unknown because he had emigrated. The age of the patients ranged from 35 years to 77 years with a mean at 60 years. In 41 cases there was histological proof that the tumour was a squamous cell carcinoma. 1 case was reported as carcinoma *in situ* (Erythroplasia of Queyrat).

Staging of Clinical Lesion

Although the local penile lesion can usually be classified relatively easily, the same cannot be said for the lymph nodes. More than 50% of patients at initial presentation have palpable inguinal lymph nodes but subsequently less than half of these are found to contain tumour (Marcial *et al.*, 1962; Williams, 1975). The remainder are infected nodes which subside after primary treatment.

Histological proof of lymph node pathology has not been possible in this retrospective survey and we have adopted the U.I.C.C. T.N.M. classification.

The N (Regional lymph node) category is as follows:

N0: No palpable lymph nodes.
N1: Movable unilateral nodes.
  N1a: thought not to contain growth.
  N1b: thought to contain growth.
N2: Movable bilateral nodes.
  N2a: thought not to contain growth.
  N2b: thought to contain growth.
N3: Fixed nodes.

Treatment

Treatment falls into 2 distinct categories (Fig. 1):

1. Where there is curative intent (Group I).
2. Where palliation is the objective (Group II).

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

The patients in Group I (33) were treated initially by either radiotherapy to the primary lesion (14) or surgery (19) (circumcision, partial or total amputation of the penis).

Group I—Curative Radiotherapy

Of the 14 patients treated by primary radiotherapy to the penis, 8 had total cure of the lesion (57%). The failed cases had secondary surgical salvage by partial amputation.

13 patients were treated with a 4 MeV linear accelerator and 1 with 300 keV X-rays. 13 were treated in the conventional manner with a perspex cylinder with wax block facings. 1 was treated with the penis strapped down over suspicious unilateral inguinal nodes.

The dose varied from 5,000 rads tumour dose delivered in 20 fractions over 28 days to 6,000 rads in 24 fractions over 32 days. The Cumulative Radiation Effect (CRE) values calculated were 1,655 to 1,896 reu. There was no relation between CRE value and the occurrence of necrosis or tumour control.

Inguinal nodes shown to contain or suspected of containing tumour were usually treated with single megavoltage fields to the inguinal regions delivering 4,000-4,500 rads in 15 treatments in 3-4 weeks. 1 patient who had bilateral inguinal and iliac nodes was treated with fields to the whole pelvis. He received a tumour dose of 4,700 rads in 15 fractions over 39 days and was free of disease 5 years later but suffered a probable pathological fracture of neck of femur due to the radiotherapy.

Radiation changes of telangiectasia, fibrosis and oedema were often seen but caused no major disability. Partial amputation of the penis for radiation necrosis was performed in 1 case. 2 patients developed urethral stenosis and 1 required regular dilatation.

2 patients with large tumours (4 × 2·5 cm and 6 × 4 cm) had persistent disease after treatment. 1 of these was obese and this made radiation to an adequate length of penis difficult. This may have contributed to the failure of treatment.

2 patients developed metastatic lymph node involvement at 2 (C. S.) and 6 (P. McM.) months' post-treatment respectively. These required irradiation of the lymph nodes. The former patient (C. S.) had this combined with systemic bleomycin.

Group I—Curative Surgery

The primary lesion was treated by circumcision (3), partial amputation (14) or total amputation (2). The lymph nodes, if palpable, were observed until the wound was healed. If the nodes had subsided, regular observation only was carried out. If the node mass was still present after

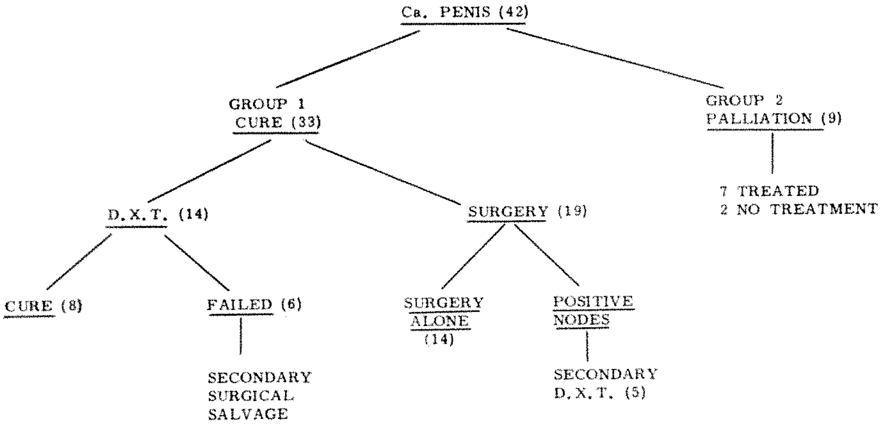

Fig. 1. Carcinoma of penis: management in 42 cases.

Table I

Results

Treatment	3-year survival		Disease sterilised	
	No.	%	No.	%
Radiotherapy	15	53	17	65
Surgery	16	50	19	63
Total	31	51·5	36	64

approximately 2 months, then secondary radical lymph node dissection or excision biopsy and radiotherapy was undertaken.

7 patients had or developed positive lymph node metastases and of these 2 had radical lymph node dissection only, 4 had radiotherapy to the inguinal node region and 1 had radiotherapy plus radical lymph node dissection. 3 patients with negative nodes before treatment developed post-treatment lymph node metastases.

The 3 patients who had radical lymph node dissection all had positive node histology; 2 are alive after 10 and 13 years, the other died after 14 months.

Group II—Palliative Surgery and Radiotherapy

The palliative cases were treated by a combination of amputation and/or radiotherapy as indicated.

9 patients were considered for palliation only. Of these, 1 patient refused treatment and 1 died before treatment could be initiated. Of the remaining 7 patients, 2 had palliative partial amputation, 3 had radiotherapy to the primary region and lymph nodes, 1 had radiotherapy to the primary lesion and 1 had radiotherapy to the primary lesion plus radical lymph node dissection. This latter patient had negative histology from the node dissection and is alive after 5 years and should probably be thought of as a cure. The remainder died of their disease within 1 to 14 months.

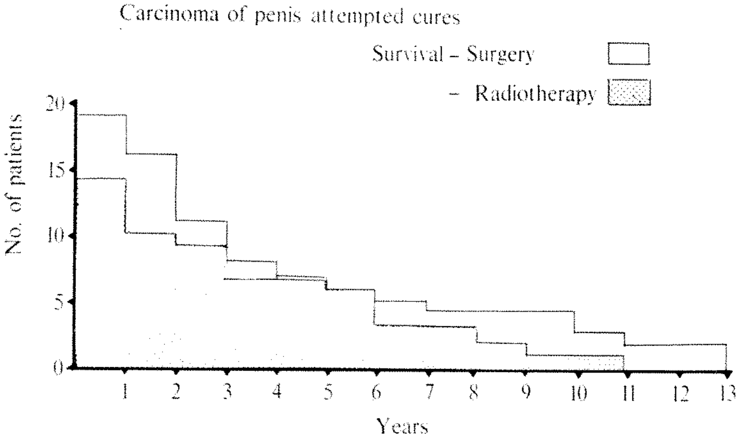

Fig. 2. Carcinoma of penis: attempted cures.

Results

The overall crude 3-year survival figures and "disease sterilisation" figures at 1 year (Jackson, 1966) are shown in Table I. The 3-year survival figures for Group I subjects alone (curative) was 62%.

Survival curves for radiotherapy and surgery (Fig. 2) show the maximum death rate in the first 3 to 4 years.

If the crude survival figures for all cases are examined according to their T.N.M. category (Table II) approximately half (20 cases) fall into the early group. The 3-year survival figures free of disease show that this early group has a much higher survival for radiotherapy than for surgery. This probably reflects the stricter criteria employed in recent years before undertaking primary radiotherapy.

If the early and intermediate groups are taken together, the 3-year survival for radiotherapy is 77·5% and for surgery 54·5%. Those figures are comparable with the 70·8% survival in the Norwegian series (Engelstad 1948).

It can be demonstrated that there is a good correlation between the T category of the primary tumour and the local cure rate (Table III).

The correlation between N category and 3-year survival clear of disease is less satisfactory but as expected gives a general indication of the prognosis (Table IV).

Table II

Staged Survival Results

	No.				3-Year survival (%)		
	Total	D.X.T.	Surgery	Nil	Total	D.X.T.	Surgery
Early T_{12}, N0, M0	20	8	11	1	58	80	43
Intermediate T_{12}, N_{12AB}, M0	12	5	7	0	70	75	66
Advanced $T_{3\text{-}4}$+	10	6	3	1	20	16	33

Table III

Correlation of T Classification with Local Cure

Classification	No.	Cures	%
T_1	25	22	88
T_2	5	3	60
T_3	6	3	50
T_4	4	1	25
Total	40	–	–

2 excluded.

Table IV

Correlation of N Classification with 3-Year Survival

Classification	No.	Cures	%
No.	16	8	50
N1A, N2A	5	3	60
N1B, N2B, +	11	5	45
Total	32	–	–

10 excluded—not reached 3 years.

Discussion

In cases where cure is the intention (Group I) definitive treatment of the penile lesion by radiotherapy has the advantage that the technique is non-mutilative and allows preservation of a functional organ in many cases. Secondary surgical salvage can be carried out if recurrence or persistence of the disease occurs. From our figures it can be seen that post-treatment lymph node involvement is no greater with radiotherapy (20%) than surgery (27%), a finding similar to other series (Jackson, 1966).

Another aspect in the management of involved lymph nodes is the use of radical lymph node dissection as compared with radiotherapy.

Our data show that of the 3 group 1 cases treated by radical lymph node dissection 2 were alive at 3 years and were free of disease. If the 1 case of radical lymph node dissection in the palliative group (Group II) is included, the overall 3 year survival is 75%.

Our early cases (T1, T2, N0, M0) treated by radiotherapy give an overall crude 3-year survival of 80%. These figures compare favourably with other series where figures of 60% (Murrell and Williams, 1965) and 78% (Pointon, 1975) have been recorded.

No other centres, however, have achieved the results of Engelstad (1948) with 89% 3-year survival in early cases where prophylactic lymph node irradiation was used in patients with no node metastases present. This perhaps merits further investigation.

Conclusion

It is concluded that the primary lesions should be treated initially, when possible, with radiotherapy followed by secondary surgical salvage if required.

Lymph node masses should be allowed to subside, and if unresolved excision biopsy carried out followed by node irradiation to positive cases.

There may still be a place for radical node dissection although the morbidity is high.

The place of prophylactic lymph node irradiation is still to be evaluated.

Summary

A retrospective survey was made of 42 cases of carcinoma of the penis presenting over 14 years.

Cases for attempted cure of the primary lesion were treated by either radiotherapy or surgery.

It is recommended that radiotherapy should be the primary treatment as it is non-mutilative, allows secondary surgical salvage where necessary and has no greater occurrence of post-treatment lymph node metastases than surgery.

We thank our colleagues for access to their patients and in particular the late Dr John Glennie of Belvidere Hospital, Glasgow.

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The Authors

P. Stewart Orr, FRCS(G), Senior Urological Registrar, Royal Infirmary.
T. Habeshaw, MRCP(UK), Registrar, Institute of Radiotherapeutics.
R. Scott, FRCS(G), FRCS(E), Consultant Urologist, Royal Infirmary.

Address for reprints: P. Stewart Orr, Royal Infirmary, Glasgow.

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The Detection and Localisation of Abdominal Lymph Node Metastases from Testicular Teratomas

W. F. HENDRY, C. J. TYRRELL, J. S. MACDONALD, T. J. MCELWAIN and M. J. PECKHAM
Testicular Tumour Unit, Royal Marsden Hospital, and Institute of Cancer Research, London and Surrey

The treatment of Stage I and II[1] testicular tumours at the Royal Marsden Hospital since 1962 has been based on the use of nodal irradiation after orchidectomy. A fundamental part of this approach has been careful clinical staging, including the routine use of lymphography. It has also been our policy to extend the field of irradiation to include the mediastinal and neck nodes whenever the lymphogram has shown clear involvement of para-aortic nodes (Smithers, Wallace and Wallace, 1971). The overall results of 10 years' experience (1962-72) of this therapeutic regime, with a minimum of 3 years follow up, have been reported by Peckham and McElwain (1976). There was a 94·7% disease-free survival rate among 127 patients with seminoma, 84·9% of 78 patients with lymphographic Stage I, and 58·6% of 29 patients with Stage II malignant teratomas were alive and disease-free. These survival figures for non-seminomatous tumours are as good as those obtained elsewhere by radical para-aortic lymphadenectomy. However, Johnson, Bracken and Blight (1976*a*) have suggested that this procedure is mandatory with testicular teratomas for pathological staging of the extent of microscopic lymph node involvement. Skinner (1976) showed that the survival rate fell from 83% (Stage B1) to 58% (Stage B2) if more than 6 histologically positive retroperitoneal nodes were found, but that the survival rate could be improved to 88% and 90% respectively with adjuvant chemotherapy.

The proposal that radical lymphadenectomy is helpful as a staging procedure in patients with testicular teratomas, if not essential for therapy, has led us to examine published and unpublished material derived from our experience at the Royal Marsden Hospital to see whether equally useful information on the detection and localisation of abdominal lymph node metastases from testicular teratomas can be obtained by other less invasive techniques. We have also considered the influence of these findings on therapy, bearing in mind that our policy is to irradiate lymph nodes one stage ahead of where the disease can be demonstrated, on the assumption that they may well contain microscopic metastases.

The Relationship between Lymphographic Changes and Prognosis

The results of pedal lymphography in 250 patients with testicular tumours treated at this hospital between 1963 and 1971 have been reported by Wilkinson and MacDonald (1975) (Table I).

Analysis of 275 patients with testicular teratomas staged and treated on the results of lymphography between 1962 and 1975 showed that approximately 80% of 110 Stage I cases compared with 60% of 44 Stage II cases were alive and disease-free at 3 years (Fig. 1). Further analysis of the Stage II cases showed that the effectiveness of irradiation and the prognosis was dependent upon the tumour volume in the para-aortic lymph nodes (Tyrrell and Peckham, 1976). In patients with metastases 2 cm or less in diameter (Stage IIA) the results of treatment were similar to Stage I, whereas of patients with larger volume metastases (Stage IIB), two-thirds developed abdominal node relapse which in most cases was associated with distant spread (Fig. 2).

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

[1] See Appendix.

Implications for Future Management

The demonstration that radiotherapy alone was unable to eradicate the disease in two-thirds of cases when the deposits in the para-aortic nodes exceeded 2 cm in diameter has led to the adoption of multimodality management for these cases (Stage IIB) and for patients with metastases in supraclavicular nodes (Stage III) (Peckham *et al.*, 1977). Treatment is initiated with chemotherapy consisting of vinblastine and bleomycin (Samuels *et al.*, 1976). If adequate regression is not achieved the treatment is modified either employing imidazole carboxamide (DTIC) with adriamycin, high dose cyclophosphamide or a combination of vinblastine, actinomycin D and methotrexate. Following chemotherapy, radiotherapy is given to para-aortic and pelvic nodes, and an elective surgical exploration is performed 4 to 6 weeks later with the aim of excising all residual bulk disease. This combined approach is also being used elsewhere (see Table II).

The surgical approach to residual bulk disease in these cases must be carefully planned, since the tumour may extend above the level of the renal vessels. It is therefore essential to define the *upper* limit of the para-aortic node mass, which may be indistinct on lymphography if mass replacement of nodes has occurred.

The Role of Ultrasound

95 patients with testicular tumours had an assessment of the para-aortic region with high-resolution ultrasound with grey-scale display. The results showed that this provided accurate information on the state of the para-aortic nodes in 69 of 77 patients (90%) in whom lymphographic, clinical or

Table I

Incidence of Positive Lymphograms in Patients with Testicular Tumours (from Wilkinson and Macdonald, 1975)

	Positive lymphograms	
Seminoma	30/116	26%
Teratoma	40/96	42%
Combined tumours	20/38	53%
Overall	90/250	36%

Table II

Results of Combination Therapy including Surgery for Advanced Metastatic Testicular Teratoma

Author	Treatment policy	No. with distant metastases	Pathology N.E.M.	No. of survivors	Duration of survival (months)
Comisarow and Grabstald, 1976	Chemotherapy + DXT →Surgery	2/11	4/11	7/11	6-48
Johnson *et al.*, 1976*b*	Chemotherapy →Surgery	7/10	7/10	8/10	2-48
Wettlaufer, 1976	Chemotherapy, Surgery, ±DXT	3/11	4/11	7/11	24-83
Merrin *et al.*, 1977	Surgery + Chemotherapy	23/37	–	26/37	Av. 14·2

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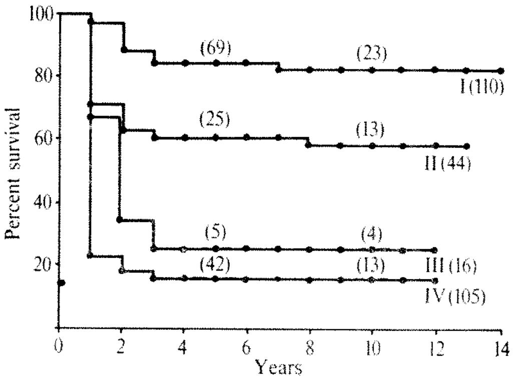

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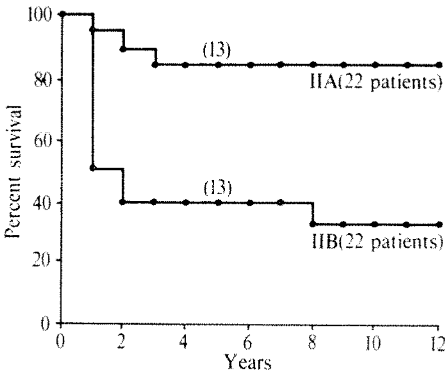

Fig. 1. Survival of patients with testicular teratoma. Royal Marsden Hospital (1964-1975).

Fig. 2. Survival of Stage II testicular teratoma patients. Royal Marsden Hospital (1964-1975).

histological confirmation was available (Table III) (Tyrrell *et al.*, 1977). Fortunately, the information provided by the ultrasound complemented the lymphographic findings, and was most valuable in defining the extent and upper limit of a large para-aortic mass when the lymphogram only indicated mass replacement.

Surgical Experience

9 patients with extensive para-aortic metastases have been explored surgically and the details are summarised in Table IV. 3 patients with seminomas had a laparotomy so that the disease could be accurately defined with clips for subsequent radiotherapy. 6 patients with metastatic teratomas had radical retroperitoneal lymphadenectomy. In 4 cases the information derived from lymphography and ultrasound indicated that the metastases were situated below the renal vessels (Fig. 3) and an anterior approach was used (Mallis and Patton, 1958). In 2 cases the disease extended up to the diaphragm and a left thoraco-abdominal approach was used, and found to provide excellent access to the tumour (Skinner and Leadbetter, 1971).

Table III

Correlation between findings on Abdominal Ultrasonography and Confirmatory Findings on Lymphography, Clinical or Histological Examination of Para-aortic Nodes in 95 Patients with Testicular Tumours (from Tyrrell *et al.*, 1977)

Ultrasound diagnosis	Lymphographic*, clinical or histological confirmation	
	Positive	Negative
Positive	43/47 (92%)	4/47
Negative	4/30	26/30 (87%)

* The lymphogram was incorrect in one case.

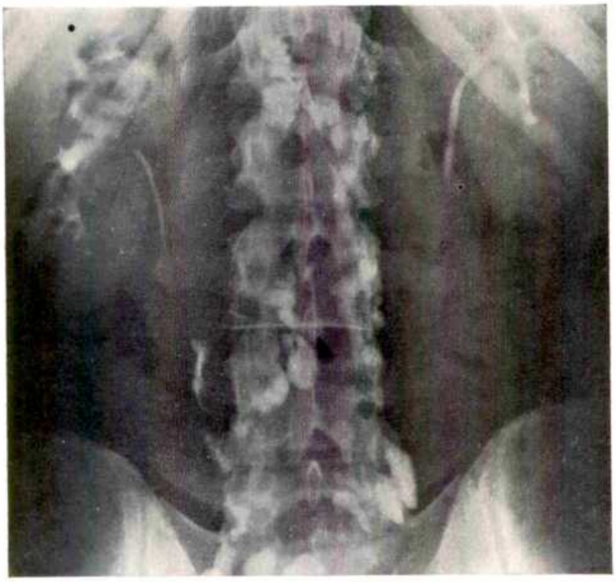

Fig. 3. Stage IIB teratoma: (*a*) preoperative lymphogram, (*b*) abdominal ultrasonography showing para-aortic nodes suitable for anterior excision, (*c*) plain X-ray with clips showing the extent of lymph node clearance.

Discussion

We believe that these results indicate that the combination of lymphography and ultrasonography provides useful information on the presence, volume and position of para-aortic lymph node metastases which facilitates the integrated approach outlined above. It is likely that the precision of tumour localisation will be enhanced by the use of computerised axial tomography and we are presently exploring the role of the scanner in this context. Since the results of irradiation are comparable with those obtained by radical lymphadenectomy in early (Stage I and IIA) cases, we do not believe that lymphadenectomy is necessary either therapeutically or as a staging procedure. Kademian and Wirtanen (1977) have shown that a positive lymphogram was correct in 28 of 29 cases (97%) on subsequent histological examination. 12 of 16 negative lymphograms (75%) were negative on pathological examination. The presence of microscopic metastases in 25% of cases with negative lymphograms is, of course, anticipated by routine irradiation of the para-aortic nodes.

Table IV

Surgical Exploration and Lymphadenectomy based on Previous Localisation of Abdominal Lymph Node Metastases

Stage	Tumour	Number	Surgical procedure	Survival (months)
IIB	Seminoma	3	Anterior mapping	3, 19 and 38
	MTI, MTU	3	Anterior lymphadenectomy	9*, 18 and 26
III	MTD, MTU	2	Thoraco-abdominal lymphadenectomy	3, 21
IV	MTU	1	Anterior lymphadenectomy	10*

* With active disease

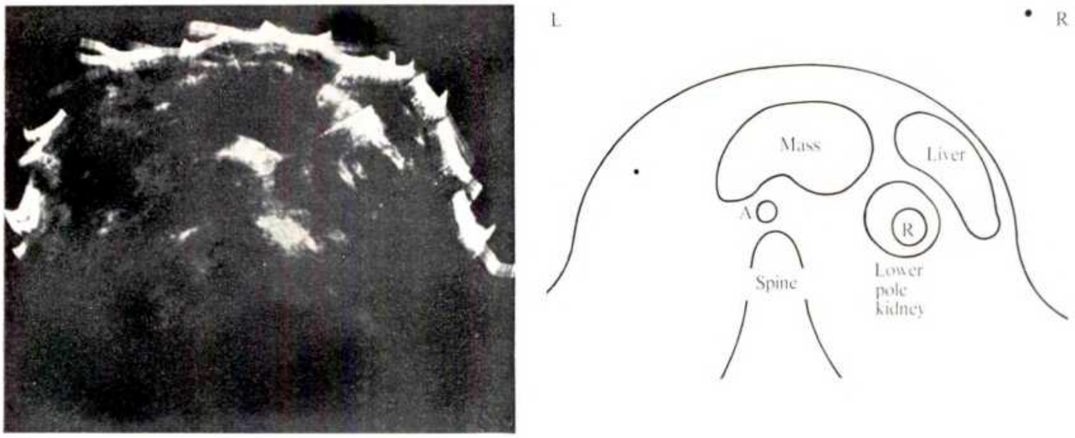

Fig. 3(*b*)

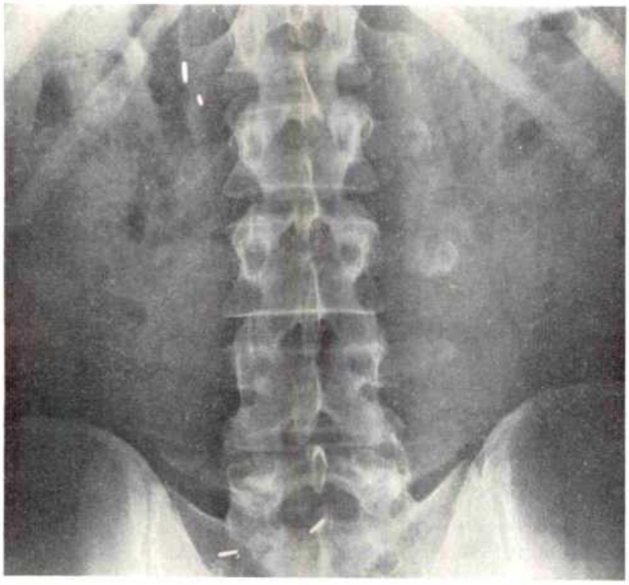

Fig. 3(*c*)

The real problem is whether the presence of extensive histological involvement of para-aortic nodes (pathological stage B2—Skinner, 1976) provides an indication for adjuvant therapy which cannot be obtained by other means. Our results indicate that the extent and volume of para-aortic node involvement as demonstrated by lymphography and ultrasonography provides information which is of comparable significance in relation to the prognosis and hence in planning treatment.

The elective role of adjuvant chemotherapy in Stage I and IIA testicular teratoma has been discussed in more detail elsewhere (Peckham *et al.*, 1977). The best method of combining chemotherapy, radiotherapy and surgery for the treatment of patients with extensive para-aortic metastases (Stage IIB) from testicular teratomas still has to be defined. There are good precedents for leaving surgery till last and using it for excision of residual bulk disease. The effective use of this sequence is totally dependent upon accurate non-operative identification of the presence and size of the metastases, and their extent and precise location must be redefined preoperatively so that the surgical approach can be planned correctly. We believe that the combination of lymphography and ultrasonography provides sufficiently accurate information for these purposes, and preliminary experience with computerised axial tomography leads us to believe that this will soon make non-operative definition of these metastases even more precise.

Summary

Review of the results of treatment of 275 patients with testicular teratomas indicates that the size of para-aortic node metastases as defined by lymphography is closely related to prognosis, and that accurate definition of these metastases is essential in planning treatment.

Although para-aortic lymphadenectomy does not appear to be necessary therapeutically or as a staging procedure, excision of residual bulk disease may be required after chemotherapy and radiotherapy. In these cases the residual para-aortic tumour mass should be accurately localised by ultrasonography so the best surgical approach can be used.

We are grateful to Miss Anthea Minchom who prepared the typescript.

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The Authors

W. F. Hendry, ChM, FRCS, Consultant Urologist.
C. J. Tyrrell, MRCP, FRCR, Lecturer in Radiotherapy (now Consultant Radiotherapist, Plymouth General Hospital).

J. S. Macdonald, DMRD, MRCPE, FRCS, Consultant Radiologist.
T. J. McElwain, MB, MRCP, Consultant Physician.
M. J. Peckham, MD, MRCP, FRCR, Professor of Radiotherapy.

Requests for reprints to: Professor M. J. Peckham, The Royal Marsden Hospital, Downs Road, Sutton, Surrey

Appendix

Current Staging Classification (Royal Marsden Hospital (Peckham *et al.*, 1977))

Stage I	Negative lymphogram, no metastases detected elsewhere.
Stage IIA	Positive lymphogram, with small volume node metastases (<2 cm maximum diameter). No metastases elsewhere.
Stage IIB	Positive lymphogram, bulky metastases (>2 cm maximum diameter). No metastases elsewhere.
Stage III	Nodes involved above and below diaphragm $\begin{cases}\text{A small volume}\\ \text{B bulky disease}\end{cases}$
Stage IVA	Minimal lung (<4 metastases).
Stage IVB	Advanced lung (>4 metastases).
Stage IVC	Extrathoracic (liver, bone, brain, etc.).

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Prolactin and Gonadotrophins in 208 Men presenting with Infertility

T. B. HARGREAVE, K. F. KYLE, ANNE M. KELLY and P. ENGLAND
Western Infirmary and Royal Maternity Hospital, Glasgow

The introduction of radioimmunoassay has faciliatted the measurement of plasma hormones and this has led to a revival of interest in the part pituitary hormones may play in male infertility. It has been established that alterations in plasma follicle stimulating hormone (FSH) and luteinising hormone (LH) may aid diagnosis in male infertility (Pryor *et al.*, 1976) and that prolactin affects the action of FSH and LH on their target organs. Hyperprolactinaemia in women is a well-recognised cause of infertility, resulting in failure to ovulate, and occurs in 15 to 20% of patients with amenorrhoea (Franks *et al.*, 1977). Some cases of male infertility with high prolactin levels and azoospermia or oligozoospermia have been reported (Thorner *et al.*, 1974; Saidi, Wenn and Sharid, 1977). This present study was undertaken to see if hyperprolactinaemia is relevant in men presenting to a general male infertility clinic.

Patients and Method

208 consecutive patients attending the male infertility clinic at the Western Infirmary, Glasgow, had blood specimens taken for assay of prolactin, FSH and LH. All specimens were separated immediately and the plasma stored at −20°C prior to analysis. A full physical examination was carried out and any abnormality recorded. Following their visit, semen samples were obtained and those with a sperm density of less than 60 million per ml had a further sample examined. If there was a wide discrepancy in these 2 analyses further samples were examined and the sperm density recorded was the best that the individual attained rather than the average density. The Comité International d'Andrologie (C.I.D.A.) have agreed a sperm density of 40 million per ml as the lower limit of normal. This definition for oligozoospermia is used in this paper, although in our own clinic we view any count of less than 60 million per ml with suspicion and our results are plotted in such a way as to show both these limits. A control group consisted of 59 men who were normal on physical examination and had a normal sperm count. In this group the sperm density was above 60 million per ml, the volume above 2 ml and the motility and morphology were normal. The average age of these men was 30 years and the average sperm density 97 million per ml.

Blood specimens were also obtained from 21 men on chronic haemodialysis complaining of impotence and infertility.

FSH, LH and prolactin were measured by radioimmunoassay using a double antibody precipitation method. The LH assay used an antiserum raised to human chorionic gonadotrophin and the reference standard was obtained from the Medical Research Council (68/69). The FSH antiserum was raised against human FSH and was obtained from Professor W. F. Butt and the reference preparation was M.R.C. 69/104. Prolactin reagents were kindly donated by the National Institute of Health, Bethesda, Maryland.

Results

Out of 208 men presenting with infertile marriages, 25 had azoospermia, 82 had oligozoospermia and 101 a sperm density of greater than 40 million per ml.

Read at the 33rd Annual Meeting of the British Association of Urological Surgeons in Aberdeen, June 1977.

Prolactin

88% of the 208 men had prolactin levels of less than 5 µg/l (Fig. 1). There were 3 cases of prolactin elevation confirmed on repeated assay (16·0, 16·8 and 37 µg/l). There was no difference in the mean prolactin levels of any of the sperm density groups. In contrast, 28% of impotent men on chronic haemodialysis had prolactin levels greater than 15 µg/l ranging from 21 to 49 µg/l.

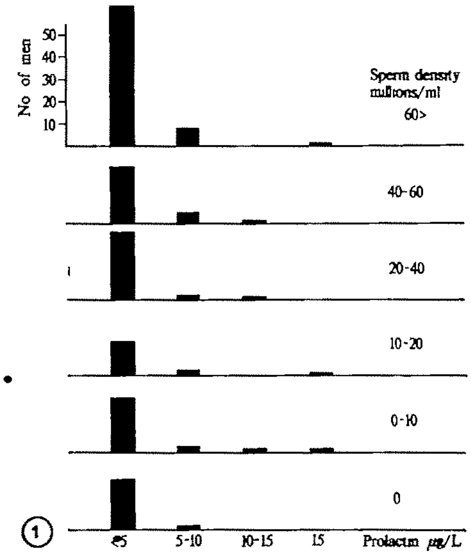

Fig. 1. Prolactin and sperm density in 208 men.

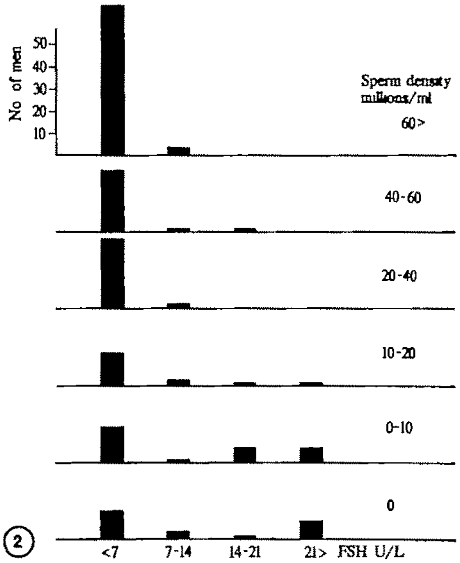

Fig. 2. FSH and sperm density in 208 men.

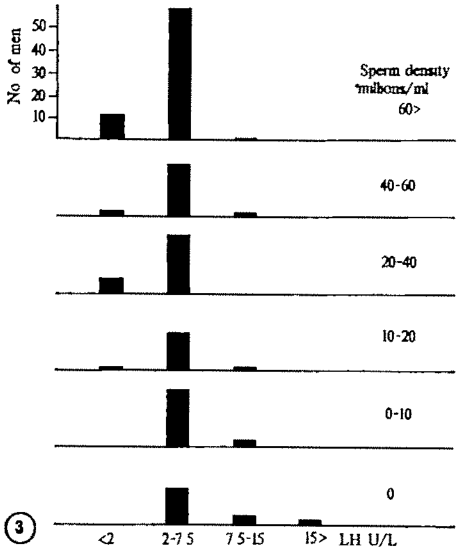

Fig. 3. LH and sperm density in 208 men.

FSH

The FSH level tended either to be grossly elevated or normal and this was most marked in the azoospermic group (Fig. 2). The mean figures tend to mask the all or none FSH elevation. There is a statistically significant difference between the FSH levels of the control group and those men with azoospermia ($P < 0·001$), and between the control group and men with a sperm density of less than 10 million ($P < 0·001$). 29 men with varicocoeles had a higher mean FSH (5·04 U/L ± 3·00) than the control group ($P < 0·001$).

LH

The values for LH showed a general shift towards the upper range of normal as the sperm density decreased (Fig. 3). 3 azoospermic men had LH levels of more than twice the upper limit of the control group (22·5, 22·0 and 17·5 U/L) and all 3 had atrophic testes on examination and on biopsy.

Discussion

208 men were referred by their general practitioners because of infertile marriages and 107 of these men (51 %) were azoospermic or had a sperm density of less than 40 million per ml. Sywer reports that the male partner is responsible for about half of infertile marriages (Bourne and Holmes, 1965) and this is in broad agreement with our findings.

We found 3 cases of prolactin elevation which were confirmed on repeated assay. In the 2 men with sperm densities above 10 million per ml the prolactin was only marginally elevated (16·0 and 16·8 μg/l). In the third man who had a maximum sperm density of 8 million per ml, the prolactin was 37 μg/l which is significantly raised. Thus in 82 men with oligozoospermia we found only 1 case of marked prolactin elevation. There was no difference between the mean prolactin levels of the control group, the oligozoospermic groups and the azoospermic group. Segal, Polishuk and Ben-David (1976) reported 2 cases of significant hyperprolactinaemia in 91 men with oligozoospermia. These workers also found a significant difference between the mean prolactin of normal men and oligozoospermic men and azoospermic men but we do not confirm this. The prolactin levels reported by Segal, however, are not directly comparable with our results. The sensitivity of our assay to elevated prolactin was shown by the control group of men on chronic haemodialysis in whom we demonstrated grossly elevated levels in 6 out of 21 men. Our results suggest that in most cases attempts to treat oligozoospermic men with bromocriptine will only alter an apparently normal hormonal state rather than revert a pathological state to normal. It is conceivable that by inhibiting a normal prolactin with bromocriptine, the action of FSH on spermatogenesis may be enhanced but preliminary results from a controlled trial on these lines in progress at the Western Infirmary are not encouraging. In those cases of azoospermia or oligozoospermia associated with hyperprolactinaemia treatment with bromocriptine has resulted in a

Table

Number of Men, Sperm Density and Gonadotrophin Levels

Number of men	Sperm density millions/ml	FSH U/L	LH U/L
59 control group	60>	3·07± 1·8	3·40±1·82
42	40>	4·1 ± 3·07	3·98±2·04
34	20-40	3·78± 2·4	3·71±1·89
19	10-20	5·92± 5·04	4·69±1·74
29	0-10	17·44±22·31	5·18±2·2
25	Azoospermia	17·42±24·35	7·02±5·76

significant increase in sperm counts and in one case pregnancy (Saidi *et al.*, 1977). Investigation of the 3 men with elevated prolactin levels has shown no evidence of a pituitary tumour; skull X-rays and pituitary tomography are in each case normal. T_3, T_4 and thyroid-stimulating hormone estimations are also normal. The significance of the prolactin elevation is not yet clear; we hope to report the results of bromocriptine treatment in the future. Our experience suggests that the part prolactin may play in male infertility is worthy of further evaluation in those centres with a specialist interest.

FSH estimation appears to be a useful diagnostic test for men with azoospermia and counts below 10 million per ml. In our series, 13 out of 29 men with sperm density below 10 million per ml had an elevated FSH and 13 out of 25 men with azoospermia. Pryor (1976) has shown that FSH elevation correlates well with testicular pathology and indicates a poor prognosis and this is confirmed by our own unpublished work.

The LH estimations show that as the sperm density drops below 20 million per ml, the LH level rises and the mean level for each group increases. We are currently investigating men with oligozoospermia and low gonadotrophin levels to see if we can detect any patients with the type of isolated pituitary gonadotrophin deficiency state reported by Marshall *et al.*, 1972.

Summary

Prolactin, FSH and LH were measured in the plasma of 208 male partners of infertile marriages. We found 1 case of marked hyperprolactinaemia in 82 oligozoospermic men (1·2%). There was no difference in the mean prolactin levels of men with normal sperm counts and men with oligozoospermia or azoospermia. One-third of the men with azoospermia and with sperm density of less than 10 million had marked FSH elevation and our experience confirms the work of others that this indicates a poor prognosis.

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The Authors

T. B. Hargreave, FRCSE, Senior Registrar, Department of Urology, Western Infirmary, Glasgow.
K. F. Kyle, ChM, FRCS, Consultant Urologist, Western Infirmary, Glasgow.
A. M. Kelly, BSc, MCB, Principal Biochemist, Biochemistry Department, Royal Maternity Hospital, Glasgow.
P. England, BSc, Senior biochemist, Royal Maternity Hospital, Glasgow.

Requests for reprints to Mr T. B. Hargreave.

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The Effect of Temperature on the Motility and Viability of Sperm

R. A. APPELL, P. R. EVANS and J. P. BLANDY
Department of Urology, The London Hospital, London

Interest in the study of male fertility has centred upon standardisation of the methods of measurement of the features in semen which are commonly thought to be important for effective fertilisation. Among these, the motility of sperm has been a notoriously weak point: observer error makes it difficult to quantify motility. Some investigators have tried to avoid the question by using an arbitrary subjective grading of "quality of motility" (Amelar, Dubin and Schoenfeld, 1973; Dougherty *et al.*, 1975; Trifunac and Bernstein, 1976).

Motility is well known to be dependent upon a number of factors, including the temperature at which the semen is kept between the time of ejaculation and the time of measurement, the presence of sperm-agglutinating antibodies, sperm-immobilisation caused by bacteria, and the lapse of time. The literature reveals wide disparities in the recommended practice in respect of temperature at which semen should be kept before it is examined. Some authorities teach that the semen should be kept at body temperature from the moment of ejaculation: Freund and Peterson (1976) recommend that the slide on which the semen analysis is to be made should be warmed to 37°C. Others have found that sperm lose their motility if stored at 37° both in the rabbit (Muehleis and Long, 1976) and in man (Dougherty *et al.*, 1975). One might suppose that sperm, like other living cells, would be better preserved by being kept at a lower temperature than normal, but many observers have found that to cool sperm to 4°C has an adverse effect on their motility. This so-called thermal shock (Mitchell, Nelson and Hafez, 1976) may be related to decreased sperm adenosine triphosphate (Mann and Lutwak-Mann, 1955) or 3′:5′-cyclic monophosphate (Tash and Mann, 1973) which may be necessary to the propagation of the flagellar wave. Cooling may also increase the viscosity of semen so much as to account for part of the diminution in motility (Freund and Wiederman, 1966). It is not clear from these studies whether cooling kills the sperm, or merely immobilises them—an effect which might be reversible given the right conditions. We set out to try to find the optimum temperature at which a sample of semen should be kept between ejaculation and the time it was examined.

Optimum Temperature for the Storage of Sperm

Materials and Methods

Semen was obtained from 42 men known to be fertile, who attended for voluntary vasectomy. Semen was obtained by masturbation after a period of abstinence corresponding to the usual coital frequency into sterile inert plastic containers (Amelar *et al.*, 1973). Specimens all had an initial sperm density $>24 \times 10^6$/ml and patients with a positive titre for plasma agglutinating antibodies (Kibrick, Belding and Merrill, 1952) were excluded.

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The semen samples were divided into aliquots and kept at 4°C, room temperature (measured to be 20°C ± 1°C) and 37°C.

After 3, 6, 12 and 18 hours from ejaculation, the following observations were made on each specimen:

1. The semen was cultured on blood agar.
2. Forward motility was determined visually at 400× magnification, counting 5 randomly selected fields of 100 sperm, and the result expressed as a mean.
3. Sperm viability was determined under oil immersion using 5% eosin and 10% nigrosin (Blom, 1950). 300 sperm were counted, and the result expressed as the percentage of live sperm.
4. Semen pH was measured with colorimetric paper, since the volumes were too small to permit the use of a pH meter.

Analysis of the data was carried out with Student's *t*-test and included a one-way analysis of variance of motility at each temperature through the 12-hour period.

Results

Motility (Table I)

When the semen was kept at 20°C there was negligible deterioration in motility after 12 hours, but there was a significant ($P<0{\cdot}01$) decrease in motility in semen kept at 4° or 37°C, the worst motility being in semen kept at 4°C. (In our material motility could not be restored by rewarming the semen.)

Table I

Motility and Viability of Sperm stored at 4°, 20° and 37°C

		Hours			
		3	6	12	18
4°C	motility %		8 ±8	7 ±5	3 ±3
	viability %		64 ±12	60 ±16	54 ±7
20°C	motility %	62 ±12	61 ±12	48 ±12	38 ±11
	viability %	69 ±15	63 ±14	51 ±11	41 ±13
37°C	motility %	56 ±13	42 ±10	24 ±10	8 ±5
	viability %	64 ±13	46 ±9	29 ±11	8 ±8

Table II

% Motility of Sperm kept at 20° and 37°C

		Hours		
		3	12	18
20°C		62 ±12	48 ±12	38 ±11
	with antibiotics	64 ±10	54 ±11	45 ±12
37°C		56 ±13	24 ±10	8 ±5
	with antibiotics	62 ±11	38 ±10	16 ±7

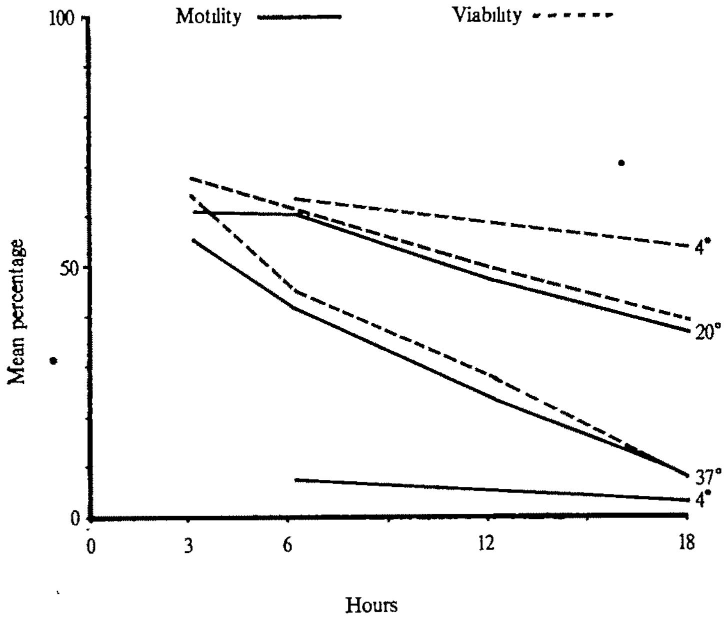

Fig. 1. Mobility and viability of sperm stored at 4°, 20° and 37°C.

Viability (Fig. 1)

Viability followed motility very closely in the specimens kept at room temperature and body temperature, but at 4°C the viability was well preserved despite the loss of motility of the sperm. At 20° and at 37°C the motionless sperms were dead, but this was not the case at 4°C.

Bacterial Growth (Fig. 2)

As expected, there was more growth at 37°C than at 20°C, and at 4°C bacterial growth was inhibited. At 37°C after 12 hours 70·3% of the specimens showed a profuse bacterial growth with with more than 10^5 colonies per ml—a figure regarded as of significance in urine cultures. The organisms found in these cultures were mainly Gram-negative bacteria (*Esch. coli* and *Proteus* species) although occasionally gram positive *Enterococci* were identified.

pH (Fig. 3)

At 37°C the semen became acidic to a significant extent ($P < 0{\cdot}001$) but pH was not significantly changed at 4° or 20°C.

Conclusion

These results led us to suppose that factors other than death of the sperm led to immobilisation when they were kept in the refrigerator at 4°C, and that if they were kept at body temperature (37°C) there was a marked deterioration in their motility accompanied by overgrowth of bacteria in the semen and a concomitant fall in pH. We considered it likely that at least part of the falling-off in sperm motility which we had observed might be caused by bacteria, or by the alteration in pH caused by their metabolism. To test this hypothesis we repeated the relevant parts of the experiment, but added antibiotics to prevent bacterial growth.

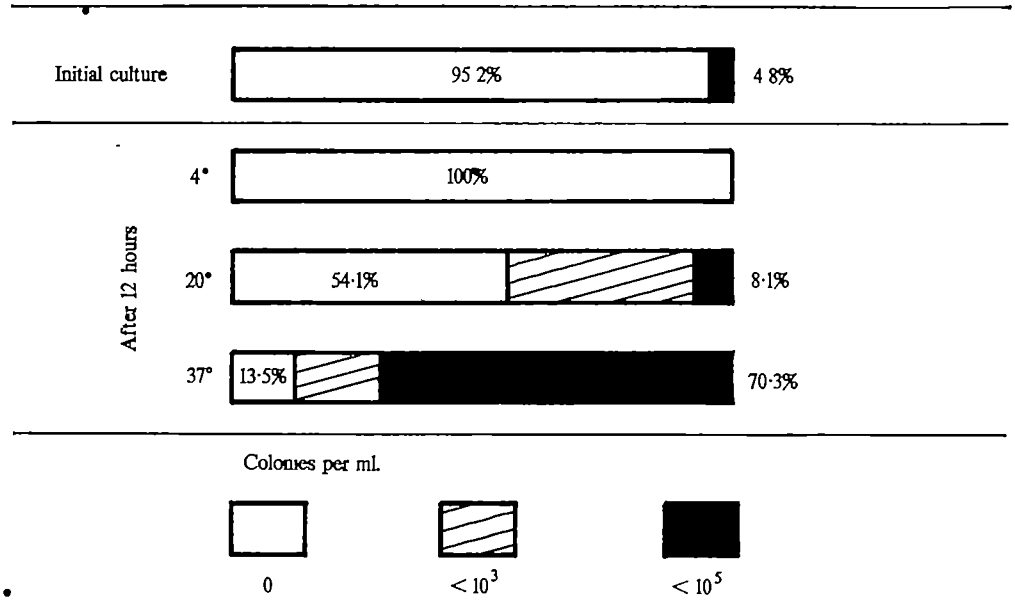

Fig. 2. Bacterial growth in semen after 12 hours at 4°, 20° and 37°C.

Storage of Semen in Presence of Antibiotics

Materials and Methods

Semen was obtained as above from 36 men attending the same vasectomy clinic. All had a sperm density greater than 24×10^6/ml and had no detectable plasma antibodies.

Specimens were divided and stored at 20° and 37°C with and without an equal volume of buffered saline containing penicillin G (1,000 units/ml) and Streptomycin (500 μg/ml) at pH 7·5 as recommended by Sawada and Ackerman (1975).

Bacteriological culture and sperm motility were determined by the methods used above, but it proved impossible to measure viability owing to an interaction between the stains and the antibiotics.

Results

None of the specimens incubated with antibiotics grew any organisms.

pH (Fig. 3)

There was no fall in pH in the semen incubated with antibiotics even at 37°C during the period of observation.

Motility (Table II)

Sperm kept in the presence of antibiotics retained their motility at 20° and at 37°C better than sperm kept without antibiotics, but there was still a significant deterioration ($P < 0{\cdot}01$) in sperm motility in the samples kept at body temperature even when bacterial growth was prevented by antibiotics.

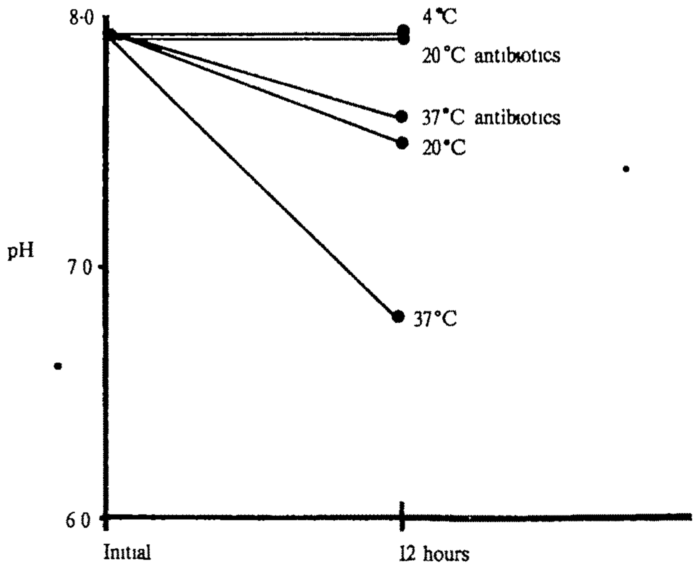

Fig. 3. Change in pH of semen kept at 4°, 20° and 37°C.

Conclusion

Although the deterioration in sperm motility at body temperature can in part be attributed to bacterial growth or the products of bacterial metabolism, there is clearly another factor related to time and temperature and independent of the presence of bacteria.

Discussion

At 4°C our studies confirmed the well-known observation that cold temperature causes a rapid falling-off in sperm motility, but we were able to show that this is not accompanied by death of the sperm, as evidence by the uptake of the vital dye eosin. From the point of view of evaluating motility of sperm in the context of the investigation of infertility, it is clearly wrong to store semen at 4°C.

Our studies also show that it is better to keep a sample of semen at room temperature, *i.e.* 20°C, than at body temperature (37°C) during the time which elapses between ejaculation and semen analysis, but they do not explain fully why this should be so. The difference in motility cannot be entirely attributed to the deleterious consequences of bacterial multiplication, since a decrease in motility occurs even when bacterial growth has been inhibited by antibiotics.

It seems likely that at body temperature sperm metabolise at a greater rate than at room temperature, and therefore use up more of the nutrients present in normal semen, and further studies are in progress to determine whether the addition of suitable nutrients may prolong the motility and viability of stored sperm. Our observations raise the question of how sperm survive the acidic pH and the warmth of the vagina before reaching the cervix where nourishment and pH conditions may promote their survival.

Summary

In specimens of semen kept at 37°C sperm lose their motility and viability. If kept at 4°C they retain their viability but lose their motility from so-called thermal shock.

The best temperature to keep semen in order to preserve sperm motility is 20°C.

Loss of motility at 37°C is not entirely prevented by prevention of bacterial contamination with antibiotics.

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The Authors

R. A. APPELL, MD, Lecturer in Urology.
P. R. Evans, Clinical Research Technician.
J. P. Blandy, DM, MCh, FRCS, Professor of Urology.

Requests for reprints to R. A. Appell, MD, Section of Urology, Yale-New Haven Hospital, 789 Howard Avenue, New Haven, Connecticut 06504, USA.

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The Clinical Significance of Antisperm Antibodies in Male Subfertility

W. F. HENDRY, HEULWEN MORGAN and JITKA STEDRONSKA
Fertility Clinic and Seminology Laboratory, Chelsea Hospital for Women, London S W 3

The concept that some men may be subfertile because they have developed auto-immunity against their own sperms has been highly controversial. Several different tests have been used to detect antisperm antibodies, but the results of these tests have not always shown a good correlation with each other, and with the patients' fertility. Shortly after we had introduced antisperm antibody tests at this hospital, the wife of one of our patients with an excellent sperm count and high titres of antisperm antibodies left him for another man and quickly became pregnant. This convinced us that further studies were necessary to define the exact clinical significance of antisperm antibodies in male subfertility. We have therefore investigated all the men attending the Fertility Clinics and looked for antisperm antibodies. The results were then correlated with the patients' clinical state and the findings on seminal analysis. When antisperm antibodies were found the behaviour of the husband's sperms was studied in the wife's cervical mucus. In order to define the significance of these findings, the behaviour of the sperms was also studied in donor cervical mucus and compared with the behaviour of sperms from donors who did not have antisperm antibodies. Finally, the antibody titres and fertility were observed while the patients with antisperm antibodies were treated with steroids.

Patients, Materials and Methods

Between September 1975 and March 1977, sera from 591 men were tested for the presence of antisperm antibodies by three techniques. Agglutinating and immobilising antibodies were assayed in serial dilutions by the techniques of Kibrick, Belding and Merrill (1952) and Isojima, Li and Ashitaka (1968) respectively. Indirect immunofluorescent studies were done by the technique of Hjort and Hansen (1971) with polyvalent (anti lgG/lgM) sheep antihuman immunoglobulin (Wellcome). Washed spermatozoa obtained from donors with at least 40 million motile spermatozoa per millilitre were used as substrate. The method of interpretation of the immunofluorescent findings has been previously described (Wall *et al.*, 1975).

All of the men submitted at least two specimens for seminal analysis. Those with counts of less than 20 m/ml, or motility less than 30% moving actively within 3 hours, were investigated and treated as previously described (Hendry *et al.*, 1973). When positive antisperm antibody tests were found, both husband and wife were examined and repeated post-coital tests were done. In addition, 44 couples were selected for crossed hostility testing on the basis of the husband's antisperm antibody results. The behaviour of the husband's sperms in the wife's cervical mucus was studied and compared with their behaviour in donor cervical mucus, while sperms from a donor with no antisperm antibodies were also studied in the wife's and the donor's cervical mucus. The details of this test and the results obtained have been described elsewhere by Morgan *et al.* (1977).

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Table I

Correlation between the Presence or Absence of Immobilising Antibodies and Titre of Agglutinating Antibodies

Titre of agglutinating antibodies	Number of patients	Immobilising antibodies		
		–	±	+
0	1	–	–	1
$<\frac{1}{32}$	17	9	4	4
$\frac{1}{32}-\frac{1}{64}$	9	4	1	4
$>\frac{1}{64}$	41	–	–	41

Table II

Correlation between the Presence and Type of Immunofluorescent Antibodies and Titre of Agglutinating Antibodies

Titre of agglutinating antibodies	Number of patients	IFT positive	Area of sperm with immunofluorescence*				
			A	E	PNC	Tail	Whole head
0	1	0	–	–	–	–	–
$<\frac{1}{32}$	17	6 (35%)	3	2	1	2	
$\frac{1}{32}-\frac{1}{64}$	9	4 (45%)	–	1	1	2	–
$>\frac{1}{64}$	41	23 (56%)	8	7	2	7	3

* See Wall *et al.* (1975).

17 men with agglutinating antibody titres more than 1 : 32 were treated with prednisone 5 mg thrice daily for 2-12 months (average 5·9 months). 17 men (including 7 patients who did not improve with the previous regime) were given methylprednisolone 96 mg/day for 7 days, as recommended by Shulman (1976). Antibody titres were checked at 3 weeks, and then repeated at 2-monthly intervals. Patients with positive seminal cultures were also given long-term low-dose antibiotic treatment according to bacteriological sensitivity studies (usually either cotrimoxazole or erythromycin 1 tablet at night for 3 months). Seminal analysis and cultures were repeated at 2-3 monthly intervals.

Results

Incidence and Correlation between Tests

Agglutinating or immobilising antibodies were found in 68 of 591 men (11·5%). The correlation between the presence or absence of immobilising antibodies and the titre of agglutinating antibodies is shown in Table I. Immobilisation was always produced by sera with positive agglutination titres of more than 1 : 64. Antibodies were detected by immunofluorescent testing in 139 of 448 patients (31%). Although these antibodies were found more commonly with increasing titres of agglutinating antibodies (Table II), the overall correlation was poor.

Table III

Results of "Crossed Hostility Testing" in 44 Infertile Couples related to Antisperm Antibody Results in the Husbands (Morgan *et al.*, 1977)

	Husbands' antibody status	Cervical "hostility"			
		Husband + wife	Husband + donor	Donor + wife	Donor + donor
Group I (22 couples)	Immobilising + agglutinating positive	21*	21*	2	0
Group II (10 couples)	Immunofluorescent positive	2	1	1	0
Group III (12 couples)	Negative	3	1	2	0

* With "shaking".

The 50 patients (8·5%) with agglutinating antibodies in a titre of more than 1 : 32 were the subject of further detailed analysis.

Analysis of 50 Patients with Agglutinating Antibodies (Titre >1 1:32)

(a) *Clinical*

The average duration of sterility was 6·3 years (range 2-18 years) and only 2 of 50 had ever produced a pregnancy in the past. 20 patients (40%) gave a past history of genito-urinary infection (9), testicular swelling (3), injury (2) or ectopia (2), vasectomy (3) or haemospermia (1). 4 patients had eczema.

(b) *Seminal Analysis*

27 patients had sperm counts of more than 20 m/ml, and in 18 of these the motility was greater than 30%. 11 patients had oligozoospermia and 5 of these had a varicocele. All specimens showed agglutination of sperms, and marked variability in the sperm counts was a noticeable feature. 12 patients had azoospermia, which was obstructive in 7.

(c) *Seminal Culture*

17 of 31 patients (55%) with antisperm antibodies had positive seminal cultures (Staphylococcus coagulase positive 8, *Escherichia coli* 8, Streptococcus group A, 1), compared with only 5 of 32 unselected patients (15%) without antisperm antibodies. None of the patients with positive cultures had any symptoms of genito-urinary infection.

(d) *Findings in their Wives*

3 patients had wives with blocked tubes which were treated surgically. Post-coital tests were never normal. Of 31 couples in whom the result was known and the husband had sperms in the ejaculate, many "dead" sperms were seen in 4, a few "dead" sperms in 12, and no sperms were seen at all in 15. Cervical "hostility" was observed in all 8 couples in whom it was sought.

(e) *Crossed Hostility Testing*

The results have been described in detail by Morgan *et al.* (1977), and are summarised in Table III. In 21 of the 22 couples where the husband had high titres of agglutinating and immobilising antibodies, the husband's sperms were unable to invade cervical mucus, either their wives' or a donor's, despite a seminal analysis which was reasonably adequate. In 10 couples where the husband had immunofluorescent antibodies, adequate penetration of cervical mucus was seen in all except 2—1 due to poor sperm motility, 1 to poor quality mucus. Similarly, adequate mucus penetration was seen in 9 of 12 couples when the husband had no detectable antibodies. Poor penetration in the other 3 couples was shown by crossed hostility testing to be due to poor sperm motility in 1 and poor quality mucus in 2.

(f) *Treatment*

5 of 17 patients treated with prednisone 5 mg thrice daily showed a distinct improvement in sperm count. In 2 patients the antibody titre fell to 1 : 32, but in no case did the antibodies disappear.

1 patient showed a dramatic improvement in sperm count, his eczema disappeared and his wife became pregnant, and delivered a normal baby.

The sperm count improved in 1 patient treated with methylprednisolone 96 mg/day for 7 days, but deteriorated in 4. The antibody titre fell to 1 : 32 in 4, but never disappeared. 1 patient with agglutinating antibodies has recently produced a pregnancy, about 6 weeks after treatment.

1 patient developed vomiting and hypotension on stopping prednisone because he failed to follow instructions for tailing it off, but otherwise no serious side-effects have so far been encountered.

Discussion

The most important question regarding antisperm antibodies in male subfertility is "do they matter?" It has been known for some years that high titres of antisperm antibodies can reduce the ability of sperms to penetrate cervical mucus (Fjallbrant, 1968). Kremer and Jager (1976) showed that this is because sensitised spermatozoa, which may have been swimming vigorously

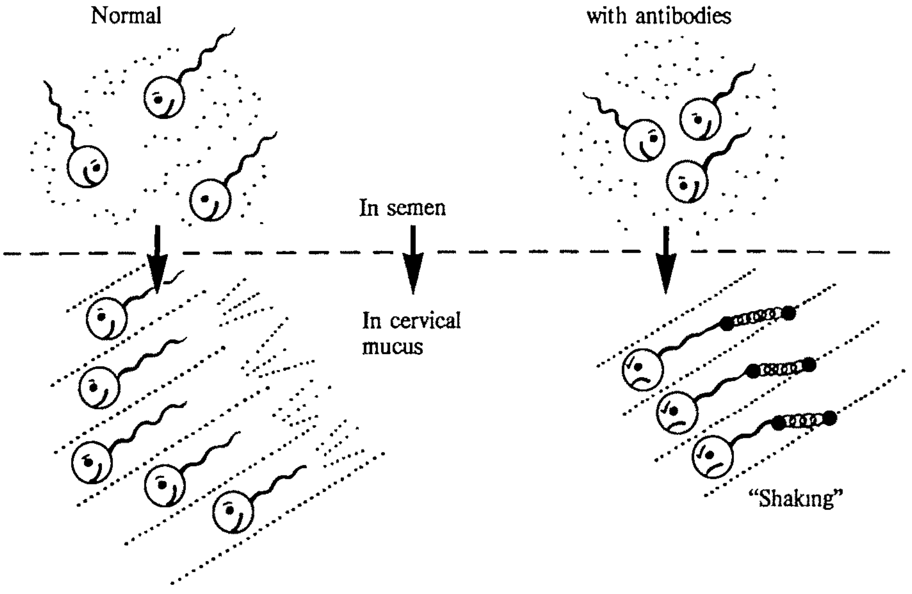

Fig. The sperm-cervical mucus contact test (SCMC test) described by Kremer and Jager (1976). Normally, the sperms form phalanges and quickly penetrate preovulatory cervical mucus. In the presence of antisperm antibodies in either husband or wife, the sperms become trapped by glycoprotein micelles in the cervical mucus and exhibit a characteristic non-progressive shaking movement.

in seminal plasma, interact with glycoprotein micelles in cervical mucus and become trapped. This produces a characteristic "shaking" movement of the sperms, which can be clearly seen in the sperm/cervical mucus contact test (Fig.). Since the shaking phenomenon is also seen if the wife has antisperm antibodies, it seemed to us that the usefulness of the test could be extended by testing the sperms and mucus against material from donors of proven fertility. The results indicated clearly that high titres of immobilising and agglntinating antibodies did prevent the sperms from penetrating cervical mucus effectively, but that this was not so with antibodies detected by the indirect immunofluorescent technique. We therefore concluded that agglutinating and immobilising antibodies were important, but we stopped doing the immunofluorescent test which appeared to have little clinical relevance (see also Johnson and Menge, 1975; Petrunia, Taylor and Watson, 1976).

There was good correlation between the presence of immobilising activity and high titres (more than 1 : 64) of agglutinating antibodies, which was identical with the conclusions of Husted (1975). If a dilution of 1 : 32 is accepted as the lower limit of significance for agglutination titres (Rumke and Hellinga, 1959) then significant titres of antibodies were found in 50/591 (8·5%) of our men, which is a rather lower incidence that the 13·4% and 17·3% reported by Halim and Antoniou (1973) and Schoenfeld, Amelar and Dubin (1976) respectively and more in accordance with the 9·6% reported by Shulman, Jackson and Stone (1975).

The couple with immunological infertility typically has a long history of infertility, probably produced by repeated encouragement based on apparently normal findings on routine investigation. A good but variable sperm count with marked agglutination, a past history of genito-urinary infection or injury, or a positive semen culture should arouse suspicion of antisperm antibodies in the husband (Fjallbrant and Obrant, 1968). An inexplicably poor post-coital test should increase the index of suspicion and observation of the "shaking" phenomenon on sperm-cervical mucus contact testing is virtually diagnostic of immunological infertility. A crossed hostility test and direct testing for the presence of antibodies is necessary to identify which partner in the marriage has the antibodies. Once the correct partner has been identified, treatment can proceed. Since the number of pregnancies achieved is inversely proportional to the antibody titre (Rumke *et al.*, 1974), treatment should be monitored by repeated estimation of titre levels. We have found steroid treatment alone to be rather disappointing, and now combine this with sperm washing and insemination (Halim *et al.*, 1974).

Summary

Sera from 591 men attending Fertility Clinics have been tested for agglutinating, immobilising and immunofluorescent antisperm antibodies.

There was good correlation between the presence of high titres (more than 1/32) of agglutinating and immobilising antobodies which were found in 50 patients (8·5%). 27 of these men had normal sperm counts, but crossed hostility testing showed that in 21 of 22 couples the sperms were unable to penetrate the cervical mucus, apparently because of the antibodies.

17 patients were treated with prednisone for an average of 6 months and 1 pregnancy was produced. 17 patients were treated with methylprednisolone for 7 days and 1 pregnancy resulted.

No correlation was found between the presence of immunofluorescent antibodies and the other antibodies or impaired sperm penetration of cervical mucus.

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The Authors

W. F. Hendry, ChM, FRCS, Consultant Urologist.
Heulwen Morgan, MB, BS, Lecturer in Gynaecology (now at St Thomas's Hospital, London).
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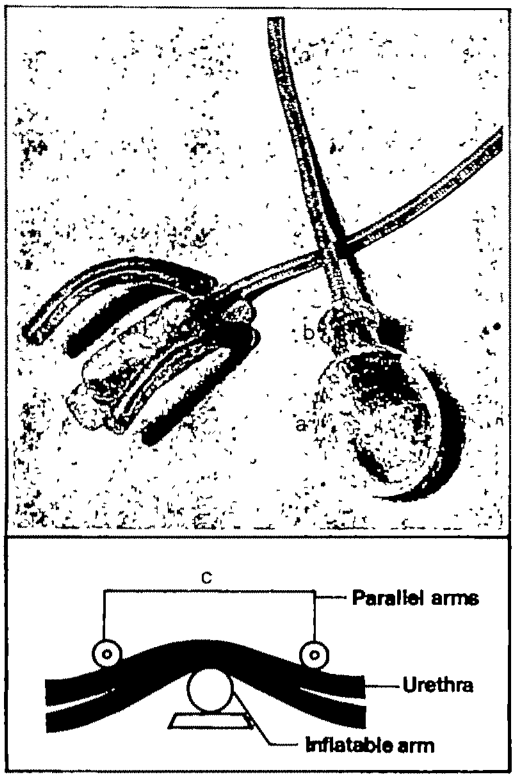

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Conversion Table—SI Units

OLD UNITS			Conversion factor Multiply by:		S.I. UNITS	
Constituent	Normal range	Units	Old to New	New to Old	Normal range	Units
Venous Blood						
Albumin	3·5–5·5	g/100 ml	10	0·1	35–55	g/l
Bicarbonate (total)	24–30	mEq/l	1	1	24–30	mmol/l
Bilirubin	0·1–0·8	mg/100 ml	17	0·059	2–14	μmol/l
Calcium	8·6–10·5	mg/100 ml	0·25	4	2·15–2·65	mmol/l
Chloride	100–107	mEq/l	1	1	100–107	mmol/l
Cholesterol	140–240	mg/100 ml	0·026	38·5	4·0–6·5	mmol/l
Creatinine	0·6–1·4	mg/100 ml	88	0·0114	55–125	μmol/l
Glucose	65–95	mg/100 ml	0·056	18	3·5–5·5	mmol/l
Iron	110–130	μg/100 ml	0·18	5·6	circa 20	μmol/l
Magnesium	1·4–1·8	mEq/l	0·5	2	0·70–0·90	mmol/l
Phosphate	2·5–4·5	mg/100 ml	0·32	3·1	0·8–1·4	mmol/l
Potassium	3·8–5·2	mEq/l	1	1	3·8–5·2	mmol/l
Protein (total)	6·5–8·0	g/100 ml	10	0·1	65–80	g/l
P.B.I.	3·75–7·5	μg/100 ml	79	0·0127	300–600	nmol/l
IgG	500–1600	mg/100 ml	0·01	100	5·0–16·0	g/l
IgA	125–425	mg/100 ml	0·01	100	1·25–4·25	g/l
IgM	50–180	mg/100 ml	0·01	100	0·5–1·8	g/l
Sodium	136–149	mEq/l	1	1	136–149	mmol/l
Transferrin	150–300	mg/100 ml	0·01	100	1·5–3·0	g/l
Triglyceride	60–140	mg/100 ml	0·0113	88·5	M2·0 P<1·5	mmol/l
Uric Acid	2–7	mg/100 ml	0·06	16·7	0·1–0·4	mmol/l
Urea	15–40	mg/100 ml	0·17	6·0	2·5–6·5	mmol/l
Arterial Blood						
Base Excess	−3–+3	mEq/l	1	1	−3–+3	mmol/l
PCO_2	32–46	mm Hg	0·135	7·5	4·5–6·0	kPa
PO_2	80–100	mm Hg	0·133	7·5	10·5–13·5	kPa
Urine Outputs/24 hr						
Calcium	200	mg	0·025	40	5	mmol
Creatinine	1–2	g	8·8	0·113	9–18	mmol
5H1AA	3–17	mg	5·23	0·19	16–90	μmol
Inorganic P.	1000	mg	0·032	31	30	mmol
Magnesium	100	mg	0·041	24	4·2	mmol
Potassium	70	mEq	1	1	70	mmol
Protein	<0·05	g	1	1	<0·05	g
Sodium	200	mEq	1	1	200	mmol
Urea	25	g	17	0·06	400	mmol
Uric Acid	500	mg	0·006	167	3·0	mmol
VMA	<7	mg	5·05	0·2	<35	μmol

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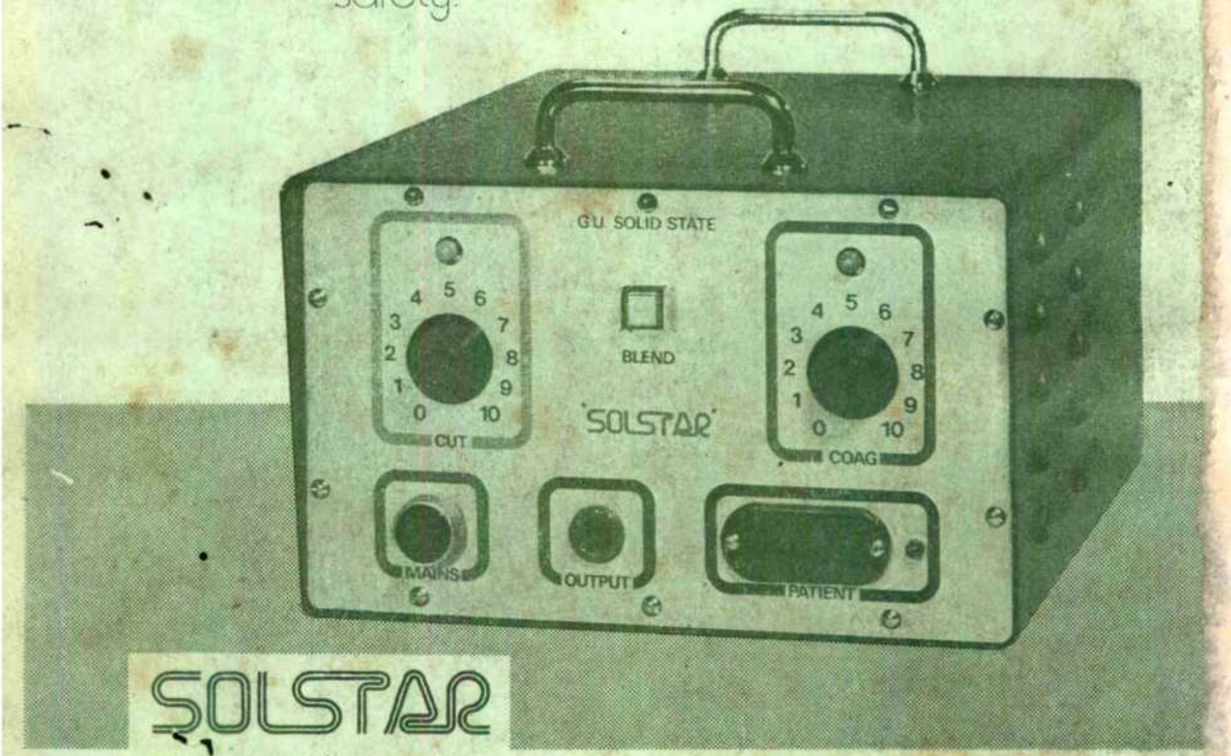

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